

HUMAN FETAL HAEMODYNAMICS

Ultrasonic assessment in normal pregnancy
and in fetal cardiac arrhythmia

Göran Lingman



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Göran Lingman

From the Department of Obstetrics and Gynecology, University of Lund,
Malmö General Hospital, Malmö, Sweden
and the Department of Obstetrics and Gynecology, Central Hospital,
Helsingborg, Sweden.

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Abbreviations and definitions

α = insonation angle

Acc time = acceleration time

Acceleration time percentage =
= acceleration time expressed in percentage of total beat-to-beat interval

AV-block = atrioventricular block

c = velocity of sound in the medium

d = depth

D = vessel cross-sectional diameter

dT/dt = temperature derivative of time

DS = descending slope

EM = electromagnetic

FHR = fetal heart rate

HR = heart rate

IVC = inferior vena cava

PI = pulsatility index

PRF = pulse repetition frequency

Q = volume blood flow normalized for ultrasonically
estimated fetal weight based on time averaged V_{mean}

Q' = volume blood flow based on time averaged V_{mean}

r = coefficient of correlation

RS = rising slope

SD = standard deviation

SV = aortic stroke volume

t = time

TD-recorder = time-distance
recorder

v = blood velocity

V_{max} = maximum blood
velocity

V_{mean} = mean blood
velocity

List of papers

- I Eik-Nes, S. H., Grip, A., Kristoffersen, K., Lingman, G., Maršál, K., Vernersson, E.: Comparison of blood flow measurements by real time/Doppler ultrasound and electromagnetic flowmeter. *Journal of Clinical Ultrasound*, (submitted, 1985).
- II Lingman, G., Gennser, G., Maršál, K.: Ultrasonic measurements of the blood velocity and pulsatile diameter changes in the fetal descending aorta. In : *Fetal and Neonatal Physiological Measurements*. (Ed.:P.Rolfe). Butterworths, Tonbridge (in press, 1985).
- III Lingman, G., Maršál, K.: Fetal central blood circulation in the third trimester of normal pregnancy. A longitudinal study. I. Aortic and umbilical blood flow. *Early Human Development* (in press, 1985).
- IV Lingman, G., Maršál, K.: Fetal central blood circulation in the third trimester of normal pregnancy. A longitudinal study. II. Aortic blood velocity waveform. *Early Human Development* (in press, 1985).
- V Lingman, G., Dahlström, J.-A., Eik-Nes, S. H., Maršál, K., Ohlin, P., Ohrlander, S.: Haemodynamic assessment of fetal heart arrhythmias. *British Journal of Obstetrics and Gynaecology* 91: 647-652, 1984.
- VI Lingman, G., Maršál, K.: Circulatory effects of fetal heart arrhythmia. *American Journal of Cardiology* (submitted, 1985).
- VII Lingman, G., Lundström, N.-R., Maršál, K., Ohrlander, S.: Fetal cardiac arrhythmia: Clinical outcome of 113 cases. *Acta Obstetrica et Gynecologica Scandinavica* (in press, 1985).
- VIII Lingman, G., Ohlin, P., Ohrlander, S.: Intrauterine digoxin treatment of fetal paroxysmal tachycardia. *British Journal of Obstetrics and Gynaecology* 87: 340-342, 1980.

The above papers will be referred to in the text according to their roman numerals.

Introduction

A. Fetal circulation

Historical and physiological background

The great Greek philosopher Aristotle (384 -322 B.C.) was the first known thinker who did not accept the contemporary belief regarding intrauterine oral nourishment. Aristotle was obviously aware of the umbilical cord as a connection between fetus and mother although this connection was not thought of by means of blood circulation.

".. its vessels deepen into the uterine wall like
the roots of a plant do into the ground and in
this way suck nourishment from the mother"
(Aristotle, 4th century B.C.)

Herophilus of Alexandria (late 4th century B.C.), as told in the writings of Galen, founded systematic anatomy soon after the death of Aristotle (Dobson, 1925). Herophilus is said to have held ideas regarding the anatomy and primary function of the umbilical cord. However, his concept divided the cord into four vessels - two veins and two arteries. Herophilus understood the connection between the veins and the hollow vein, the course of the great artery along the spinal column and the cord arteries alongside the bladder of the fetus. He considered the vessels to carry material for blood and breath to the fetus (Dobson, 1925). The concept of blood circulation had still to come, however.

Erastritos of Coe (330 - 257 B.C.), who is regarded as the first scientific physiologist, came very near to discovering the blood circulation (Dobson, 1925). Herophilus and Erastritos established the connection between the fetus, umbilical cord and the placenta. This connection was later confirmed by Galen of Pergamon (129 - 99 B.C.) (Dobson, 1925). The concept of the fetoplacental unit was thus established.

It was not until the 16th and the 17th centuries, however, that fetal physiology made further progress. Hieronymus Fabricius (1562 - 1604) Professor of Anatomy at the renowned school of Padua, discoverer of the function of the venous valves, described also the anatomy of the fetal lamb. He made drawings of the human fetal heart, lungs, liver, IVC, and the foramen ovale (Dawes, 1964).

The fundamental physiological intrauterine situation could not be considered as understood, however, until the modern concept of the blood circulation had won acceptance. Therefore some of the historical background to the understanding of blood circulation is given in the following.

Jean Fernel in Paris made in 1542 the fundamental observation that the cardiac systole and diastole coincided with expansion and contraction of the arteries, respectively (Cournand, 1964). Andreas Caesalpinus (1519 - 1603) described the importance of the pumping character of the heart, of the valves and the blood circulation to the lungs. He is considered by one source to be the first to use the word "circulation" concerning the blood supply to the lungs (Salvadori, 1984). This term was earlier used in alchemy.

William Harvey (1578 - 1657) had studied at the school of Padua 1600 -1602. From this, the leading school of Europe at that time, he probably acquired his basic knowledge of physiology, being a pupil of Fabricius (Hamilton & Richards, 1964). After making extensive animal experiments with well defined inquiries, Harvey presented his results in 1628 in *Exercitatio anatomica de motu cordis et sanguinis in animalibus*. In this great tome Harvey set out the modern concept of blood circulation. Harvey expressed doubts about generalizing findings from one species to the another, findings considering the passage of the blood from the right side of the heart to the left. These doubts were raised by the fact that there are more species without lungs than with them. Harvey described the fetal circulation with the utmost accuracy, the foramen ovale and the ductus arteriosus, how the blood passes through them and how they close after birth (Hamilton & Richards 1964). He was obviously well aware of the fact that fetal and maternal blood did not mix in the placenta (Dawes, 1964). Detailed information on how the oxygenated blood mixes with non-oxygenated blood in the fetus was still lacking however.

The preferential direction of the well-oxygenated blood from the placenta was suggested by Sabatier (1778) who claimed that all of this blood was directed through foramen ovale to the left heart and via the ascending aorta to the myocardium and the brain. The venous blood flow from the superior vena cava then passed to the right heart via ductus arteriosus to the placenta. The reason for this distinct separation was, according to Sabatier, the existence of a well-defined anatomical structure, namely the Eustachian valve, the membranous structure found in the upper part of the IVC close to the right atrium. A different opinion had been expressed two years earlier by Wolff and Becker (1776) who claimed that two-thirds of the oxygenated blood in the IVC was shunted to the left heart. This thesis was based on anatomical studies.

Already Fabricius in Padua (16th century) had used fetal lambs for his investigations. More sophisticated experimental set-ups with fetal lambs were presented in 1884 by Cohnstein and Zuntz. They tried to measure umbilical blood flow by connecting a flowmeter - *Stromuhr* - to the cut umbilical cord. A flow in the

umbilical artery of $0.016 \text{ ml} \cdot \text{g}^{-1}$ fetal weight and min was found (Barcroft et al., 1934). By also measuring blood gases in the umbilical cord, one could get some idea of fetal oxygen consumption. Cohnstein and Zuntz (1884) found experimental proof for gas exchange between the mother and the fetus over the placenta, thus confirming the observation by Schehl in 1798 that the blood in the umbilical vein was red and in the artery more bluish (Huggett, 1927). However, the results could not be considered reliable as the method by Cohnstein and Zuntz per se changed the circulation gravely.

Huggett (1927) presented results from experiments on fetal goats performed under more physiological conditions than before. The experiments demonstrated the method of acute exteriorization, where a cesarean section made the fetus available for the experiments, the umbilical cord and the placenta being kept intact. This technique has since been widely used in fundamental research on fetal physiology - research of great value to our understanding of the intrauterine life of the human fetus. Huggett (1927) measured O_2 saturation and CO_2 content in the umbilical artery, the fetal aorta and carotid artery. He concluded that there was a gas exchange over the placenta and estimated the diffusion gradients of oxygen and carbon dioxide. He found evidence supporting Wolff's theory (Wolff & Becker, 1776) concerning the directions of the blood flow.

Barcroft and co-workers (1934) published experimental results on the cardiac output of the fetal goat. A cesarean section and a thoracotomy on the fetus made it possible to measure the cardiac minute volume. Estimations of the cardiac stroke volume varied between 0.21 and 1.43 ml in embryonal ages ranging between 12 weeks 5 days to 21 weeks 3 days. The output per minute and g fetal weight was found to be astonishingly constant during gestation (median 0.155, range 0.12 - 0.18 $\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) (Barcroft et al., 1934). A third of the cardiac weight-corrected minute volume was considered to be directed to the placenta - these flow values to the placenta were higher than those measured by Cohnstein and Zuntz (1884). Barcroft et al. (1934) concluded that the ratio of blood flow through the heart to the fetal weight varies little as also does the oxygen consumption in the fetus during the latter half of pregnancy.

In 1937, Barclay and Franklin presented a cinéangiographic film showing the blood flow in veins of adult animals after contrast injection (Dawes, 1964). Barcroft realized the applicability of the method to his own field of research. By the collaboration between the two groups the method was applied on the fetal lamb (Barcroft et al., 1939). Contrast medium injected in the superior vena cava was directed solely to the right atrium, and when injected into the umbilical vein, passed

the IVC to enter mainly the left atrium via the foramen ovale but also to some extent the right heart. Again, Wolff's theory was supported and the relations and directions of the different parts of blood returning to the fetal heart were experimentally clarified.

That same year, 1939 Barcroft presented more important, results from the intensive experimental research performed by his group. He criticized the invasive nature of the technique performed earlier by his own group (Barcroft et al., 1934). A new, less invasive technique was now used in which the fetal lamb was kept *in utero* while blood samples for gas analysis and flow calculations were taken from the umbilical vessels. Blood flow in the umbilical cord was calculated to a range of 56.8 - 218.2 ml · min⁻¹ · kg⁻¹ in fetuses of 111 - 152 days.

Systematic measurements of blood flow in fetal vessels had still not been performed with complete reliability however. In 1949 Cooper and Greenfield used a plethysmograph in which the lamb fetus was placed, still connected to the mother by the umbilical cord. The umbilical veins were occluded and the volume decrease of the fetus was measured (Cooper & Greenfield, 1949). Umbilical blood flow in the fetal lamb was estimated to 130 ml · min⁻¹ · kg⁻¹, a result close to that obtained by Barcroft (1939). It is also in agreement with results from fetal lambs obtained by Dawes (1962) who used an EM flowmeter to measure umbilical vein flow and of the same magnitude as results obtained by groups using modern Doppler ultrasound technique for measurements at the corresponding site in the human fetus (Gill, 1979; Eik-Nes, 1980; Wladimiroff, 1981; Griffin, 1983; Jouppila, 1984).

Dawes (1968) provided the field of fetal physiology with important data based on experimental studies on exteriorized and on chronically instrumented fetal lambs. Important experimental studies on lamb fetuses were performed also by Assali (Assali et al., 1965) and Rudolph (Rudolph & Heymann, 1976).

Knowledge of the human fetal circulation was earlier based mainly upon anatomical studies. Haselhorst and Stromberger (1932) presented a method for measurement of blood circulation time through the placenta namely the dye-dilution technique. They injected a solution of Congo red dye into the cord of the human fetus immediately after birth and took blood samples after varying intervals. Haselhorst and Stromberger concluded that 60 s was the time required for the blood to circulate through the human placenta at the moment of birth. They also estimated the O₂ consumption of the fetus at birth. Stembera and Hodr used glucose dilution (1963) and thermodilution (1964) post partum in the same way. They found a decreased circulation in the placenta of asphyxiated newborns.

The first experimental studies on central blood circulation in human fetuses were made by Lind and Wegelius (1949) in connection with legal abortions. The fetuses, being of 12 -25 weeks of gestation, were removed by cesarean section with intact membranes. An incision was then made in the membranes and contrast infused in the umbilical vein. An x-ray exposure sequence was taken of the fetus during the infusion. It could be clearly seen that the blood from the IVC was divided into a large left heart stream and a small right heart stream (Lind & Wegelius, 1949, 1954). After contrast infusion into the jugular vein, the predominant part passed out via the pulmonary artery. The directions of the blood in the central part of the body were thus elucidated in the human fetus.

With the increased interest in pregnancy supervision, attention now focused on human fetal heart activity. Carr and McClure (1931) were probably the first to present a case of auscultated fetal cardiac arrhythmia - a case of fetal tachycardia. Cremer (1906) had already presented the first human fetal electrocardiogram. This technique was utilized in a modification by Hon (1959) for the study of fetal heart rate patterns and by Hon and Huang (1962) in a study of fetal cardiac premature and missed beats. These were considered as "benign", which was later supported by others (Komáromy et al., 1977; Kleinman et al., 1983), while the contradictory opinion was expressed by Stewart et al. (1983). Fetal supraventricular tachycardia was also initially considered to be a type of arrhythmia which was not associated with an increased fetal risk (Levkoff, 1969) whereas others later reported fetal and neonatal complications (Schreiner et al., 1978) and indications for intrauterine treatment were discussed (Valerius & Jacobsen, 1978).

Introduction of ultrasound technique into Obstetrics made possible detailed anatomical and functional studies of the human fetal heart (Winsberg, 1972; Baars & Merkus, 1977; Wladimiroff et al., 1979). The improved resolution of the commercially available ultrasound equipment stimulated rapid development of the field of fetal echocardiography during recent years (Wladimiroff et al., 1984).

B. Doppler ultrasound

a. Historical background

Christian Doppler (1803 - 1853) presented in 1842 his paper "Ueber das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels" before the Royal Bohemian Society of Learning (Doppler, 1843). He described an increase in the

frequency of waves on water, of sound and of light as the observer approaches the source and a decrease if the observer moves away from the source. This finding was called the "Doppler theory" by the Dutchman Buys-Ballot (Buys Ballot, 1845 a,b). Buys-Ballot was the first to confirm the theory experimentally and stated the concept of the "Doppler effect" in acoustics.

Pierre Curie who, together with his brother discovered the piezoelectric effect 1880, had a student by the name of Paul Langevin. The catastrophe of the *Titanic* in 1912 clarified for Langevin the need to develop techniques for detecting underwater obstructions. In 1917 he managed to construct a quartz crystal transducer which could generate ultrasound waves. This construction was developed and used mainly during the Second World War for submarine hunting under the name SONAR system (White, 1976). The Doppler theory proved valid also for ultrasound (White, 1976).

Doppler ultrasound technique was first used for detection of cardiac activity in adults by Satomura (1957) who applied it simultaneously with electrocardiogram and phonocardiogram. The same author used the technique also on peripheral vessels (Satomura, 1959)

Lindström and Edler (1969) presented blood flow registrations over the mitral valve by means of continuous wave Doppler technique in an experimental model using calf heart. They found that the valve opening preceded the flow. The clinical application was elucidated in a study comprising 40 patients with various cardiac diseases and 10 normal subjects (Edler & Lindström, 1969).

b. Physical background

A sound receiver moving towards the source perceives a tone with a higher frequency than the actual frequency of the emitted tone. Conversely, when the receiver moves away from the source a tone with a lower frequency will be perceived. The same effect, the Doppler effect, will be found when the source approaches or moves away from the receiver, respectively. The difference between the emitted frequency and the received frequency is called the Doppler shift frequency. This effect is also valid for sound inaudible to the human ear - sound at frequencies above 20,000 Hz, i.e. ultrasound. An ultrasound beam is generated according to the piezoelectric effect by a crystal in a transducer, vibrating when supplied with an electric charge. The vibrations generate the ultrasound at various given frequencies, depending on the properties of the crystal. For diagnostic purposes, frequencies of 1 - 10 MHz are used. When an ultrasound beam of a given

cells, the backscattered ultrasound will return with an altered frequency. The difference in frequency between the emitted and reflected ultrasound, (fd), will be proportional to the velocity (v) of the blood according to the Doppler equation:

$$fd = \frac{2 \cdot f_0 \cdot v \cdot \cos\alpha}{c}$$

is the insonation angle, i.e. the angle between the ultrasound beam and the direction of the blood and c the ultrasound velocity in the tissues.

The two main types of Doppler ultrasound mode are the continuous wave technique and the pulsed wave technique. The transducer for continuous wave ultrasound consists of two crystals, one emitting crystal producing a continuous beam of ultrasound and one crystal receiving the reflected or backscattered ultrasound (Hatle & Angelsen, 1981). The pulsed wave transducer consists of only one crystal emitting ultrasound in pulses. When it does not emit the ultrasound pulses it functions as a receiver. A gate is opened a shortly after the pulse emission in order to receive the backscattered echoes from a nearby target and after a longer time to receive the echoes from a distant target. The lag between pulse emission and the opening of the gate is the time it takes for the ultrasound pulse to travel through the tissues to the target, and return. This principle enables a depth resolution, i.e. measurement of blood velocities in vessels at different depths, which is not possible with the continuous wave technique. The ultrasound pulses are emitted with certain pulse repetition frequencies (PRF). The maximum blood velocity measurable or the highest Doppler shift (fd_{max}) detectable is related to the PRF and the ultrasound velocity in tissue (c) according to the formulas:

$$fd_{max} = \frac{PRF}{2} \quad \text{and} \quad v \cdot d < \frac{c^2}{8f_0}$$

One disadvantage connected with the pulsed wave technique is thus the limited possibility of measuring very high blood velocities. This limit is governed by the PRF and varies according to the sampling depth. The maximum PRF for a sampling depth d is decided according to the relation:

$$PRF_{max} = \frac{c \cdot d}{2}$$

where c is the approximate sound velocity in tissue.

The size of the sampling volume, i.e. the volume from which the Doppler shift is recorded, is determined by the length of the emitted ultrasound pulse and the width of the ultrasound beam, the latter being defined by the crystal size. The optimal insonation angle, i.e. the angle between the ultrasound beam and the vessel's direction, is 0 or 180 degrees. However, in clinical practice it is difficult to achieve a measurement in the direction of the blood flow. On the opposite when using an insonation angle of 90° no Doppler shift is detectable at all. At angles close to 90° the Doppler shifts are small; therefore an insonation angle of less than approximately 60° is preferable for reliable Doppler shift detection.

For further details on the physics of Doppler ultrasound see White (1976) and Hatle and Angelsen (1981).

c. Fetal application

Callagan presented (1964) the Doppler ultrasound applied to the detection of heart movements in the human fetus. Robinson (1972) applied pulsed Doppler ultrasound for the same purpose.

McCallum (1977) made the first blood waveform analysis of the blood velocity signals recorded from the umbilical artery by applying continuous wave Doppler ultrasound to the umbilical cord after delivery. The same year, Fitzgerald and Drumm (1977) succeeded in obtaining blood velocity signals from the umbilical arteries *in utero* by means of continuous wave Doppler. In 1978, McCallum used pulsed wave Doppler ultrasound for the same purpose. Gill (1978) made measurements of blood velocity in the intraabdominal part of the umbilical vein of the fetus.

In 1980 the first measurements of blood velocity and flow in the fetal descending aorta were obtained by means of the combined pulsed Doppler and real-time ultrasound technique introduced by Eik-Nes et al. (1980). The method combines in a simple way two commercially available instruments and has been used by several investigators (Wladimiroff & McGhie, 1981; Jouppila & Kirkinen, 1984). As the method is so recently investigated, few normal materials on blood velocity and flow in human fetuses have been presented (Tonge et al., 1984; Jouppila & Kirkinen, 1984; Maršál et al., 1984), very few on the physiological developmental changes during the course of normal pregnancy (Eldridge & Berman, 1983; Erskine & Ritchie, 1985) and none on the intrauterine distribution of flow.

The combined ultrasound method enables detection of the blood velocity signals from the fetal descending aorta and assessment of peripheral vascular resistance and fetal cardiac performance by using waveform analysis in a way similar to that used in adults (Gosling et al., 1976; Hatle & Angelsen, 1981). The relation to gestational age of the parameters characterizing blood velocity waveform is not yet known however.

The circulatory effects of fetal cardiac arrhythmia can be evaluated by means of the combined ultrasound method as previously demonstrated (Maršál et al., 1980). By using the experimental model which fetal heart arrhythmia simulates, important aspects of fetal cardiac physiology could be studied. The validity of Frank-Starling's law for the fetal heart had been questioned (Rudolph & Heymann, 1974), with the background of experiments on fetal lambs. The applicability of this law to the human fetal heart was asserted in 1980 (Maršál et al.), using arrhythmia as a model.

Aims of the investigation

To evaluate the non-invasive Doppler ultrasound technique for measurement of volume blood flow and to compare it with an established, invasive method - the EM method, in a study on domestic pigs.

To study the time relation of the pulsatile vessel diameter and the blood velocity in the human fetal aorta and to assess to what extent a possible time difference in occurrence of these events affects the calculation of volume blood flow.

To investigate the blood velocity, vessel diameter and volume blood flow in the descending aorta and in the umbilical vein of normal fetuses.

To follow the physiological developmental course of the fetal blood flow and its distribution during the last trimester of pregnancy.

To study longitudinally the blood velocity waveform parameters recorded from the descending intrathoracic and abdominal aorta of fetuses in the third trimester of normal pregnancy.

To evaluate three non-invasive methods for diagnosing and examining of the haemodynamic consequences of irregular fetal heart activity, namely abdominal fetal ECG, phonocardiogram and combined pulsed Doppler and real-time ultrasound.

To apply the combined ultrasound technique to fetal heart arrhythmia, as this simulates an experimental model enabling the study of physiological and pathophysiological mechanisms of the fetal heart.

To investigate the clinical relevance of fetal arrhythmia for the outcome of pregnancy.

To present a method for intrauterine conversion of a specific type of arrhythmia using transplacental digoxin treatment.

Material

A. Animal study

In the animal experimental study (I), domestic pigs were used for the comparison of the non-invasive Doppler ultrasound technique versus the invasive EM flowmeter. The pigs were healthy, weighing 22-25 kg. Two pigs were used for training in the operative procedure and 3 were used for the simultaneous measurements of the aortic blood flow using the 2 techniques.

B. Human studies

In the methodological study investigating the time relationship of the pulsatile vessel diameter changes and the blood velocity (II), 10 human fetuses were examined. Their gestational ages ranged between 36 and 40 weeks, according to ultrasound fetometry in early pregnancy. All ten pregnancies were normal.

In two studies, fetal volume blood flow (III) and aortic blood velocity waveform (IV) were studied longitudinally in 31 pregnant women in the third trimester of pregnancy. Ten women had to be excluded from the study as various complications occurred (pre-eclampsia, premature labour, placental abruption). The 21 remaining pregnancies with normal course and outcome thus constituted the study group.

Possible non-invasive tools for haemodynamic evaluation of fetal heart arrhythmia were presented in study V, in which the methods were applied to two human fetuses with severe cardiac arrhythmia. The 2 pregnant women were healthy, 32 and 30 years old, respectively. Both were followed in their otherwise normal pregnancies from the 25th gestational week till term. These women both delivered in the 39th gestational week female infants weighing 2910 g and 2750 g, respectively. The former delivered vaginally after a spontaneous labour, while the latter was delivered by cesarean section due to fetopelvic disproportion.

Haemodynamic effects of the fetal cardiac arrhythmia (VI) were examined with the combined ultrasound technique in 37 pregnant women. The women were either referred to our Ultrasound Laboratory from other obstetric units or from our Antenatal Clinic when irregular fetal heart sounds were detected. Median maternal age was 28 years (range 19 to 23 years). Median gestational age at the time of the fetal

blood flow measurements was 34 weeks (range 22 to 40 weeks); all but one of the pregnancies were ultrasonically early dated. Median gestational age at delivery was 40 weeks (range 35 to 42 weeks). Thirty-two women delivered vaginally after spontaneous labour. Five were delivered by means of cesarean section on the indications: fetal tachycardia and imminent heart failure in 2 cases, maternal bronchial asthma in one, fetopelvic disproportion in one, and fetal distress in labour in one case. 19 newborns were females and 18 males. Median birth weight was 3380 g (range 1600 - 4610 g) . 31 neonates had an Apgar score ≥ 8 at 1 min and ≥ 9 at 5 min while 3 had an Apgar score ≤ 7 at 1 min and 2 had ≤ 7 at 5 min. One fetus died *in utero* after 40 postmenstrual weeks; section revealed a large ventricular septum defect and a suspected chromosomal aberration. While still alive *in utero* the fetus showed a grade III AV-block.

During 6 years, 113 cases of fetal cardiac arrhythmia from six obstetric units were evaluated (VII). Maternal and neonatal parameters are given in Table I.

In paper VIII, intrauterine digoxin treatment of a fetus with arrhythmia is described. In a 25-year-old healthy nullipara, fetal arrhythmia was heard in the 29th gestational week. The woman was delivered vaginally after spontaneous labour in the 38th gestational week. The infant, a healthy girl weighing 3050g, had Apgar score 7 at 1 min, 8 at 5 min, and 10 at 10 min.

Table I. Maternal and neonatal background parameters in 113 pregnancies with fetal heart arrhythmia

Type of arrhythmia	N	Maternal parameters		Neonatal parameters		
		Maternal age (years)*	Nulliparae/multiparae	Male/female	Gestational age at birth (weeks)*	Birth weight (g)+
Supraventricular arrhythmia	94	27 (18-43)	47/47	41/53	40.0 (33-42)	3283 (742)
Atrioventricular block	5	31 (24-40)	0/5	3/2	40.5 (37-42)	2970 (303)
Ventricular arrhythmia	14	26 (20-43)	7/7	3/11	38.0 (37-40)	3605 (598)
Total	113	27 (18-43)	54/59	47/66	40.0 (33-42)	3309 (720)

* Median and range. +Mean and SD.

Methods

A. Technical equipment and measuring procedure.

Electromagnetic flowmeter. A Blood Flow Meter 376 (Nycotron A/S, Drammen, Norway) was used for the comparative animal study (I). Probes of appropriate internal diameters were applied on the abdominal aorta of the pig for optimum fit. The analogue signals were recorded of the instant flow and of the time-averaged integral of the flow. An electronic integrator also gave digitally the absolute blood flow. The probes were calibrated both *in vitro* and *in vivo*. The former calibration was performed by applying the probes on plastic tubes flushed with saline. The *in vivo* calibration was done by clamping the aorta 20 cm proximal to the probe and infusing 500 ml of blood distal to the clamping site; blood sampled from the animal's own jugular vein was used. The zero level was obtained by clamping the aorta. The zero level was also ascertained by turning the flowmeter on and off.

Phonocardiography. The fetal phonocardiograms (V) were recorded by using a microphone (Siemens-Elema, Stockholm, Sweden) placed on the maternal abdomen over the fetal heart.

Abdominal fetal ECG. A commercial electrocardiograph (Siemens-Elema, Stockholm, Sweden) with an additional amplifier was used for recordings from the fetuses with cardiac arrhythmia (V, VII, VIII). Registrations were obtained from silver electrodes placed on the maternal abdomen. During labour and delivery, direct fetal ECG was recorded from the fetal scalp (HP 80 300 A Hewlett-Packard, GmbH, Boeblingen, FRG).

The abdominal fetal ECG used for synchronization the aortic flow velocity and the aortic diameter curves (II) was obtained by another fetal electrocardiograph (Teltec, Lund, Sweden) with an ultra-sensitive amplifier modified from the design of Wheeler et al. (1978).

Ultrasonic measurement of fetal vessel diameter. The pulsatile fetal aortic diameter changes were measured using a digital pulsed echo tracker with a phase-locked loop system (Teltec, Lund, Sweden) connected to a 3 MHz real-time linear array scanner (ADR, Model 2130, Advanced Diagnostic Research Corp., Tempe, Arizona) (Gennser et al., 1981) (II). The spatial resolution of the system was 30 μm with 1.28 kHz repetition frequency at 10 cm depth. The output signals were recorded on a polygraph (Recomed 330 - P, Hellige GmbH, Freiburg, FRG). The vessel diameter measurement was performed by using a TD-recorder (Teltec, Lund, Sweden)

(Lindström et al., 1977) on frozen real-time images (I,III,V,VI). The TD-recorder enables measurement of the vessel diameter in 0.4 mm steps, from the outer border of the proximal vessel wall echo to the inner border of the distal wall echo. The mean of ten consecutive measurements was used for the calculation.

Non-invasive fetal blood flow measurements. Blood flow measurement was performed by means of a combined real-time and pulsed Doppler ultrasound technique (Eik-Nes et al., 1984). The actual vessel, i.e. the aorta or the umbilical vein, was located with a 3.5 MHz real-time linear array ultrasound scanner (ADR, Model 2130 Advanced Diagnostic Research Corp., Tempe, Arizona). The blood flow velocity in the vessel was measured with a multifrequency pulsed Doppler instrument (ALFRED, Vingmed A/S, Oslo, Norway); an ultrasound frequency of 2 MHz was used and 100 Hz high-pass filter for the elimination of disturbances from the vessel wall movements. The pulse repetition frequency (PRF) was automatically optimized by the instrument between 9.5 and 5.2 kHz, depending on the sampling depth. Blood velocities in vessels could be measured down to 15.8 cm from the Doppler transducer. The highest measurable velocity at that depth was $126.8 \text{ cm} \cdot \text{s}^{-1}$ at an insonation angle of 45° . The width of the sample volume was decided by the slightly focused crystal with diameter of 10 mm. The length of the sample volume could be set to 5 or 10 mm; for vessels with diameter less than 10 mm the shorter sample volume length was used.

The Doppler transducer was firmly attached to the real-time transducer at a fixed angle of 45° (Fig. 1). This arrangement enables correction of the recorded blood

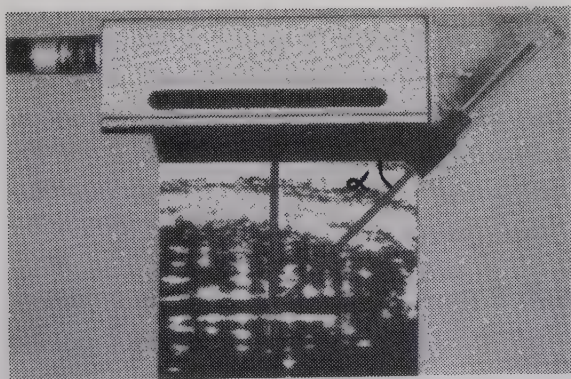


Figure 1. The real-time ultrasound transducer with the pulsed Doppler transducer attached at a fixed angle of 45° . The course of the Doppler beam is marked in the real-time image of a longitudinal section of the fetal body with the descending aorta.

velocity when the real-time transducer is held parallel to the vessel, by dividing the velocity by the cos of 45°, giving the blood velocity in the vessel direction. A footswitch was used to alternate momentarily between the two ultrasound modes. The direction of the Doppler ultrasound beam was marked by a line on the real-time image. The depth of the vessel from the Doppler transducer was measured to facilitate the positioning of the sample volume.

The control of the primary Doppler signals excluding interference with other vessels and to ensure an optimal positioning of the sample volume were performed in three ways. A Doppler spectrum analyser (DAISY, Vingmed A/S Oslo, Norway) gave on-line a Doppler shift spectrum printed out on a fibre-optic recorder (Linescan, Honeywell, Denver, Colorado) and displayed on an oscilloscope (Hewlett-Packard 1225 A Display X-Y, Hewlett-Packard, Colorado Springs, Colorado) for visual control. The primary signals were also checked by ear, using stereo, high fidelity headphones (HD 414 X, Sennheiser, Wedemark, West Germany); the positive Doppler shifts were heard on one side and the negative ones on the other.

Doppler shift signals were analysed on-line by estimators built into the Doppler instrument, giving output signals of the maximum and the mean blood velocity. The mean blood velocity signals were time-averaged continuously by a moving 3 s window. The Doppler instrument provided calibration signals for each output channel. The analogue signals were outwritten on a polygraph (Recomed 330-P, Hellige GmbH, Freiburg, FRG) (paper speeds 25 mm · s⁻¹ in III, IV, V, VI; 50 mm · s⁻¹ in I; 100 mm · s⁻¹ in II).

The time-averaged mean blood velocity over at least 10 s and the mean vessel diameter were used to calculate the volume blood flow in ml · min⁻¹ according to formula:

$$Q' = \frac{V_{\text{mean}} \cdot \pi \cdot D^2}{\cos 45^\circ \cdot 4}$$

Fetal weight estimation: Ultrasonically measured biparietal and mean abdominal diameters of the fetus were used to estimate of the body weight; formula according to the method described by Eik-Nes et al. (1982), modified by Geirsson and Persson (1984).

Waveform analysis. Waveform analyses of the maximum blood velocity (II, IV, VI) and of the synchronized aortic diameter changes (II) were performed by means of a digitizer (Hipad TM Digitizer, Bausch & Lomb, Houston Instrument Division,

Houston, Texas) and a micro-computer (ABC 806, Åtvidaberg, Sweden) with a curve-fitting program. The limit resolution of the digitizer was 0.1 mm.

Equations were fitted to the blood velocity curve according to the least-square method. The first part of the curve was always fitted to a linear function and the part of the cycle following peak to an exponential function. Twenty points for each section of the curve were marked, constituting the input data for the computerized analysis. The waveform parameters calculated according to the curve-fitting program, are defined in Fig. 2 and Table II .

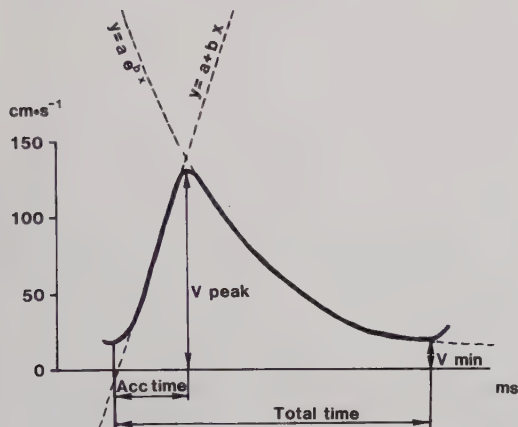


Figure 2. Schematic drawing demonstrating waveform analysis of the fetal aortic maximum blood velocity. V_{peak} = peak velocity; V_{min} = minimum velocity after the peak; Acc. time = acceleration time (start -to-peak time).

PI (Gosling et al., 1971), RS and DS (McCallum et al., 1978) were all normalized for the integrated mean blood velocity over the beat, making them independent of the insonation angle.

Table II: Blood velocity waveform parameters.

$$PI = \frac{V_{peak} - V_{min}}{V_{mean}}$$

$$RS = \frac{b}{V_{mean}} \quad (y = a + bx)$$

$$DS = \frac{b}{V_{mean}} \quad (y = ae^{-bx})$$

B. Design of investigations

Animal study (I): The narcosis of the pigs was induced with intravenously administered thiopentone sodium (Pentothal^R, Abbott, 20 mg · kg⁻¹). The pig was intubated and ventilated with 70% nitrous oxide. To maintain the narcosis, Pentothal^R (50-100 mg/dose) and fenatyl (Leptanal^R, Leo, 0.2 mg/dose) were given. The abdomen of the anesthetized pig was opened along a midline incision. The intestines were removed from the duodenum to the sigmoid colon. All branches of the abdominal aorta including all lumbar arteries were ligated from below the renal arteries to the aortic bifurcation. The arterial pressure was recorded continuously with an intravasal catheter inserted into the femoral artery. The EM probe was placed near the aortic bifurcation at right angles to the aorta. The size of the probe was chosen for optimal fit to the vessel walls. The abdomen of the pig was thereafter filled with saline to get a medium for the ultrasound and to some extent imitate the intrauterine situation.

The blood velocity in the abdominal aorta of the pig was measured by Doppler ultrasound 3 cm proximal to the EM probe. The aortic diameter was measured by means of the TD-recorder at the same site. EM recordings of the blood flow and ultrasonic measurements of the flow velocity were performed simultaneously. The flow was altered pharmacologically with dextran 70 (Macrodex^R, Pharmacia), vasopressin (Postacton^R, Ferring AB), atropine and propranolol (Inderal^R, ICI).

Human studies: (II-VI). All women participated in the examinations after giving their informed consent. The ultrasonic measurements of the blood flow in human subjects have been approved by the local ethical committee. The fetal blood flow measurements were performed with the women in a semirecumbent position tilted 15° to the left to avoid the vena cava syndrome. Recordings of fetal blood flow were performed solely during periods of fetal apnéa and absence of fetal movements. Only signals of optimal quality were accepted and used for the evaluations. The women were asked to abstain from smoking 1 hour before the examination.

In study II, the pulsatile diameter changes and the mean blood velocity in the intermediate part of the fetal descending thoracic aorta were subsequently measured by the pulsed echo-tracker and the combined real-time and pulsed Doppler technique, respectively. The curves were synchronized by recording the abdominal fetal ECG. The fetal QRS complexes were used for selection of equal beat-to-beat intervals ($\pm 5\%$). The calculations were based on eight cardiac cycle pairs in each fetus. Fifty

synchronized sections per cycle of the aortic diameter and the blood velocity were integrated. The aortic stroke volume (SV) was calculated according to the formula:

$$SV = \frac{t \int V_{\text{mean}} \cdot \pi \cdot D^2}{\cos 45^\circ \cdot 4}$$

The SV was related to the ultrasonically estimated fetal weight (see above). Volume blood flow was estimated from the SV and FHR ($Q = SV \cdot FHR$). From Q, an "effective" diameter was calculated:

$$D_{\text{eff}} = \sqrt{\frac{4 \cdot Q}{V_{\text{mean}} \cdot \pi \cdot 60}}$$

In the two longitudinal studies (III, IV) on fetal blood flow and blood velocity waveform, measurements were performed in the intermediate part of the fetal descending thoracic aorta and in the abdominal aorta 1 - 2 cm proximal to the bifurcation. In study III, measurements were also performed in the intraabdominal part of the umbilical vein. From the volume blood flow at these three measurement sites it was possible to calculate the distribution of the flow to the lower extremities and viscera of the fetus and to the placenta. The examinations were performed every other week from the 27th till the 40th completed gestational week. Measurements were made both upstream and downstream at all three sites. Waveform analysis of the maximum blood velocity curve (IV) in the fetal descending aorta was performed. The parameters given above and the averaged aortic stroke volume were determined.

In study V, three non-invasive methods; - abdominal fetal ECG, fetal phonocardiogram, and ultrasonic blood flow measurement - were applied in 2 cases of severe fetal heart arrhythmia.

The combined ultrasound method was used for the study of the circulatory effects of various kinds of fetal arrhythmia (VI). Volume blood flow and blood velocity waveform in the descending thoracic aorta were studied.

Intrauterine fetal digitalization was performed when indicated in cases of fetal cardiac arrhythmias (VII, VIII). This was done by giving the mother 0.25 mg digoxin (Digoxin^R, ACO) intravenously twice on the first day of treatment and thereafter 0.25 - 0.5 mg orally a day.

The statistical analyses of the results were performed with the BMDP (Biomedical Computer Programs, UCLA, Departement of Biomathematics, California) using t-tests and variance analysis.

C. Critique of methods

EM method: This method has been widely used in basic experimental fetal research (Dawes, 1968; Assali et al., 1965). However, if used with less than the utmost care the method is open to many errors. Probes having nonhomogeneous electromagnetic field may give false results (Dawes, 1968). An improper application of the probe on the pulsating vessel can be another source of error. The internal diameter of the probe has to correspond to the vessel size. However, the pulsating vessel changes its size and a slight constriction of the vessel by the probe is unavoidable. This constriction can cause alterations in the flow pattern, change the flow in the vessel (Dawes, 1968) and influence the arterial blood pressure (MacDonald, 1974). In the present study (I) care was taken to use probes with optimum fit. The EM flowmeter is sensitive to turbulence in the blood flow; for reliable measurements the flow should be axial symmetrical (Wyatt, 1968). This is not certain in the upper thoracic aorta (MacDonald, 1974) in contrast to the abdominal aorta, chosen for measurements in study I. If the probe is applied obliquely on the vessel, false results will be obtained (Wyatt, 1968). Therefore, the right angle of the probe position was repeatedly checked (I).

The main weakness of the EM flowmeter - a problem with multifactorial etiology - is the base-line error. The change in base-line when switching the magnet on and off should not exceed 1% (Dawes, 1968). A technique to set the zero flow level is to obstruct the vessel distal to the site of measurement. This produces a zero flow without causing collapse of the vessel. In the present study (I) the occlusion was done proximal to the probe. Nevertheless, as the electromagnetic field was pulsed, a non-occlusive zero determination was also performed and found to be consistent with the zero obtained with the occlusion. A proper calibration of the flowmeter is essential. In the present study this was performed both *in vivo* and *in vitro*.

Despite the above-mentioned critique the EM technique is considered the most reliable invasive reference method for continuous measurements of blood flow if one has sufficient regard for the sources of error (Dawes, 1968; Wyatt, 1968).

Abdominal fetal ECG: When recordings of good quality are obtained, abdominal fetal ECG is valuable in the diagnosis of fetal heart arrhythmia. However, the P wave can not be found in the traces from those leads. In pregnancies up to the 32nd-33rd gestational week, there can be difficulties also in obtaining adequate signals of the QRS complexes (Wheeler et al., 1978). The evaluation of a fetal ECG

tracing can be complicated by interference by disturbing noise which may alter the shape of the QRS complexes. This problem is aggravated when weak fetal ECG signals are amplified. Despite the difficulty in recognizing their shape, the QRS complex can be used to distinguish between the extrasystoles of atrial and ventricular origin.

A bad signal/noise ratio can to some extent be circumvented by the use of filters which, however, may alter the shape of the QRS complex further. In study II the filtered ECG signals were used only for the timing of the recordings.

Combined ultrasound technique for measurement of fetal blood flow: This method is associated with many sources of error if used without due care and knowledge. "Pathological" blood velocity traces can be simulated and false blood flow values obtained if these errors are not recognized, or accepted.

False results of the mean and the maximum blood velocities can be due to errors in the insonation angle. It has been shown that a trained operator can keep the correct insonation angle within 5° (Eik-Nes et al., 1984). The maximum error in the volume flow calculated from the mean blood velocity is then 9%. The velocity waveform parameters used in the present studies are, however, by definitions, independent of angle.

The blood velocity can be erroneously estimated due to interference by signals from the nearby vessels. When measuring in arteries, this source of error affects mainly the registered mean blood velocity and not the maximum blood velocity, as the venous blood velocity interferes with the estimate of the former continuously and with the latter only when it exceeds the maximum velocity in absolute value. This can be caused by the use of a too large size and an incorrect positioning of the sample volume. Too low values of the velocity estimates will be obtained even without interfering signals when the sample volume is positioned in the outer parts of the vessel, resulting in a serious error, especially in vessels with parabolic flow profiles, e.g. in the umbilical vein. In vessels with flat blood velocity profiles, e.g. the thoracic descending aorta, this problem is a minor matter as the difference between the mean and maximum velocities is small. The estimate of the mean blood velocity is more sensitive to all the above errors than is the maximum velocity. The errors can be minimized by careful checking of the primary signals, by means of Doppler shift spectrum analysis, and by audial and visual control of the output signals as done in the present set-up.

Overestimation of the mean blood velocity can occur when a high-pass filter with a too high cut-off level is used (Eik-Nes et al., 1984). In the present set-up, a cut-off level of 100 Hz was used, corresponding to the blood velocity of $5.4 \text{ cm} \cdot \text{s}^{-1}$ at 45° insonation angle. The filter effect is most expressed in vessels with a parabolic flow profile, e.g. in the umbilical vein. Therefore a correction for the filter effect on the estimate of mean blood velocity in the umbilical vein was done by $2.7 \text{ cm} \cdot \text{s}^{-1}$ corresponding to half of the cut-off level (Gill, 1979). In the fetal descending aorta all velocities exceed the cut-off level during the systole, whereas the flow profile is more blunt in the diastole, then probably containing velocities cut by the filter. The amount of cut Doppler shift frequencies is very difficult to calculate but is probably relatively low. Nevertheless, this phenomenon might result in a slight overestimation of the mean blood velocity in the aorta too. The maximum blood velocity is less often affected by the filter as it usually exceeds the cut-off level. The blood velocity might be affected by the filter in cases of severe fetal compromise (Lingman et al., 1983). In these cases the filter effect exerts its influence more on the mean than on the maximum velocity.

Another source of error is the aliasing phenomenon which occurs when the Doppler shift frequency exceeds 2 PRF (Hatle & Angelsen, 1979). Blood velocities above this level will erroneously be recorded as negative resulting in underestimation of the mean and maximum velocities. This is seldom a problem when measuring blood velocity in the fetal descending aorta with the present Doppler flowmeter (ALFRED, Vingmed A/S, Oslo, Norway) as the blood velocity is not that high and the flowmeter automatically optimizes the PRF for different depths of sampling. There is, however, a depth range of approximately 14-16 cm at which this risk is obvious at high blood velocities. In practice this depth of sampling is very rare. Using Doppler shift spectrum analysis, the aliasing phenomenon can be detected and false interpretation of the results avoided.

A major source of error in the calculation of the volume blood flow is the vessel diameter measurement. Any error in this calculation will be squared in the volume blood flow results (see above). It has been demonstrated earlier by our group (Eik-Nes et al., 1984) that this error can be kept below 0.4 mm causing a maximum error in the volume blood flow of 13-10% for blood vessels having a diameter within the range of 6-8 mm. Measuring diameters of small vessels results in an unacceptable flow error. Correct placing of the calipers on the real-time image of the vessel walls is difficult due to the appearance of the echo complexes. Therefore, the well-defined

proximal borders of the echo complexes were used and the diameter thus measured from the outer to the inner aspects of the vessel.

Another source of error is the calculation of the vessel cross-sectional area from the vessel diameter, assuming the vessel to be circular. This is a wrong assumption concerning the descending aorta, as the aorta expands non-symmetrically. The size of this error is probably small but the present measuring technique does not allow estimation of its precise magnitude.

The volume blood flow is related to the ultrasonically estimated fetal weight introducing another source of error. In the investigation studying volume blood flow changes (III), the fetal weight was on average overestimated by 3.2% (SD 8.5) which lowers the resulting weight-related volume blood flow somewhat.

When using velocity waveform analysis of the maximum velocity curve for evaluation of the fetal circulation, most of the described errors (e.g. the insonation angle, interference problem, positioning of the sample volume, filter effects, diameter measurements and ultrasonic estimation of fetal weight) are minimized.

The results of the volume blood flow measurements show a wide variation (III). This might be due to physiological variations, fetal interindividual differences, and operator intra- and interindividual differences. Operator intra-individual differences were investigated in a momentary reproducibility test by measuring blood velocity in two directions at the same site (III, IV). This did not result in any significant differences. The operator interindividual reproducibility was investigated in a specific study on 8 fetuses (unpublished). Three operators measured blood velocity, aorta diameter and fetal weight in random order and combination. The results were subject to analysis of variance (Table III); significant difference was only found in diameter measurement ($p < 0.05$). The results of this test indicate the difficulties of estimating volume blood flow. In study III all measurements of volume blood flow were performed by one person to eliminate the interindividual error.

Table III. Significance of difference of the aortic blood flow parameters measured in an interindividual reproducibility study (48 observations in 8 term fetuses).

Parameter	Significance of difference (p)
Blood velocity	0.450
Vessel diameter	0.046
Fetal weight	0.468
Blood flow	0.107
Pulsatility index	0.680

D. Ultrasound safety aspects

Doppler ultrasound technique for fetal diagnostics has been used and available since 1964 (Callagan et al., 1964). Many investigations on possible hazards of the technique have been performed. However, the results of only a few studies are transferrable to human fetal conditions. Up to the present time, there is only one recommendation concerning the output energy intensities of ultrasound equipment - the Statement of the AIUM (American Institute of Ultrasound in Medicine) Bioeffects Committee (1978). Few manufacturers of commercially available ultrasound scanners and Doppler instruments, including manufacturers of CTG apparatuses and detectors of fetal heart sounds, are able to present reliable values of output energy levels. Besides, it is often unknown which parameter of energy is referred to (Table IV).

Table IV. Definitions of intensity parameters of ultrasound output energy (WHO 1982)

SAPA = Spatial average-pulse average intensity = The pulse average intensity averaged over the beam cross-sectional area
SATA = Spatial average-temporal average intensity = The temporal average intensity averaged over the scan cross-sectional area on a specific surface
SPPA = Spatial peak-pulse average intensity = The value of the pulse average intensity at the point in space where the pulse average is a maximum or is a maximum within a specified region
SPTA = Spatial peak temporal average intensity = The value of the temporal average intensity at the point in the acoustic field where the temporal average intensity is a maximum within a specified region
SPTP = Spatial peak-temporal peak intensity = The value of the temporal peak intensity at the point in the acoustic field where the temporal peak intensity is a maximum, or is a local maximum within a specified region

The following mechanisms of interaction between ultrasound and biological tissue have been described:

Thermal: The ultrasound can increase temperature in the tissues. In soft tissue with a density of $1 \text{ g} \cdot \text{cm}^{-3}$ and with a specific heat/unit mass of $1 \text{ cal} \cdot \text{g}^{-1} \cdot ^\circ\text{C}^{-1}$

and with an absorption coefficient of $0.1 \text{ Neper} \cdot \text{cm}^{-1}$ the dT/dt is $0.048 \text{ }^{\circ}\text{C} \cdot \text{s}^{-1}$ at a SATA intensity of $1 \text{ W} \cdot \text{cm}^{-2}$ (WHO 1982).

Cavitation: The intrinsic pressure in the tissue can subsequently decrease and increase with the ultrasound waves which can initiate formation and changing of gas bubbles. The *stable* cavitation can occur when gas bubbles already exist in the tissue. Compression and decompression of the bubble can damage the cell membranes, cause microstreaming around the bubbles and change the internal relationship of intracellular organelles (WHO, 1982). Such effects have been shown in water at intensities about $300 \text{ mW} \cdot \text{cm}^{-2}$ (WHO, 1982). *Transient* cavitation can cause collapse of gas bubbles at higher intensities and tissue damage at intensities of $1\text{-}2 \text{ W} \cdot \text{cm}^{-2}$ (WHO, 1982). Ter Haar and Daniels (1981) found the cavitation phenomenon in guinea-pigs at SATA intensities of 80 and 680 $\text{mW} \cdot \text{cm}^{-2}$ with 0.75 MHz continuous-wave ultrasound.

Acoustic streaming: When an ultrasound beam is travelling through a liquid, the liquid can start oscillating. This phenomenon was demonstrated by Selman and Jurand (1964) showing disorganization and recovery of endoplasmic reticulum at intensities of $8\text{-}15 \text{ W} \cdot \text{cm}^{-2}$ at 1 MHz ultrasound.

Stress mechanisms: Effects of varying pressures in tissue depending on the ultrasound field viscosity-variation forces, can initiate spinning and relative movements of intracellular bodies, in relation to the surroundings (WHO, 1982).

These main mechanisms have been demonstrated in plant cells, cell cultures and animals. Moore et al. (1982) showed a tendency to decreased birth-weight of babies exposed to ultrasound *in utero*. In this study, not all factors causing lower birth-weight were taken into account and it was not established that the ultrasound was the causative factor. Concerning human fetal chromosomal anomalies, no causal effects have been demonstrated for diagnostic ultrasound (WHO 1982).

Considering the available literature, the WHO (1982) referred to the guidelines presented by AIUM (1978): "In the low megahertz frequency range there have been no independently confirmed significant biological effects in mammalian tissues exposed to intensities (SPTA) below $100 \text{ mW} \cdot \text{cm}^{-2}$. Furthermore, for ultrasonic exposure times less than 500 s and greater than one second, such effects have not been demonstrated even at higher intensities, when the product of intensity and exposure is less than 50 joules $\cdot \text{cm}^{-2}$." AIUM (1979) comments: ".... an SPTA intensity of $100 \text{ mW} \cdot \text{cm}^{-2}$ forms a reasonable basis for discussion."

The pulsed Doppler set-up used in the present studies, was evaluated concerning output energy intensity, by two independent laboratories. The commercially available

Doppler flowmeter (ALFRED) was modified with a resistance box on the output contact of the transducer in order to reduce the energy for the fetal examinations. A SATA intensity of $27 \text{ mW} \cdot \text{cm}^{-2}$, SPTA intensity of $103 \text{ mW} \cdot \text{cm}^{-2}$, SPTP and SPPA intensities in the order of 1000 and $800 \text{ mW} \cdot \text{cm}^{-2}$, respectively, were found. Periods of 15-20 s were used for the blood velocity measurements at each site. Diameter and body size measurements were performed on frozen real-time images. The SATA output intensity of the real-time scanner is stated by the manufacturer to be $0.2 \text{ mW} \cdot \text{cm}^{-2}$. The search for the vessels lasted only a few seconds. Thus the output energy and the exposure time can be considered to be very low with the present mode of measuring (Carson, 1978).

Results and comments

A. Animal methodological study (I)

Fifty-seven, 21 and 18 simultaneous measurements of aortic blood flow with the Doppler technique and the EM method were performed in 3 pigs. Arterial blood pressure ranged 99 to 169 mm Hg and HR 86 to 174 beats $\cdot$ min⁻¹. The mean blood velocities measured by the Doppler ultrasound technique ranged between 5 and 92 cm $\cdot$ s⁻¹; the mean aortic diameter between 3.7 and 8.7 mm and the mean blood flow between 60 and 1400 ml $\cdot$ min⁻¹. The correlation coefficients (r) of the results obtained with the two methods in the 3 pigs were 0.98, 0.89, and 0.91, respectively. The Doppler method overestimated the flow measured with the EM method by 12.1%, probably due mainly to the 100 Hz high-pass filter used. This overestimation seemed to be more pronounced when comparing the low blood velocity range, due to the fact that the high-pass filter then exerts a greater influence on the estimation of mean blood velocity. The shape of the curves obtained by the EM method was astonishingly like the shape of the velocity curves obtained by the Doppler method.

The depth of the vessel from the ultrasound transducer was 8-12 cm, which was approximately the same as in the measurement situation of the human fetus in the third trimester of pregnancy. The size of the abdominal pig aorta and the pig HR also corresponded to the human fetus.

Similar agreeing results of flow obtained by Doppler ultrasound and EM technique were described by Avasthi et al.(1984) and Reneman et al. (1973) who measured the blood flow in the canine renal artery. It thus seems that the non-invasive Doppler ultrasound technique is useful for blood flow measurements and gives reliable results.

B. Human methodological study (II)

In the study on the time relationship of the mean blood velocity curve and the aortic diameter curve, the mean FHR based on beat-to-beat intervals was 135.5 (SD 4.9) beats $\cdot$ min⁻¹. The time-integrated mean blood velocity was 33.0 (SD 4.4) cm $\cdot$ s⁻¹ and the mean systolic and diastolic aortic diameters were 7.3 (SD 1.1) and 6.3 (SD 1.1) mm, respectively. The onset of the diameter curve was somewhat earlier than that of the mean velocity curve; the mean difference was 7 ms (SD 9) which was near the resolution limit for the digitizer and was not significant. An inverse time relationship was found for the peak of the mean blood velocity and the systolic

diameter. The peak mean blood velocity preceded the systolic aorta diameter by 37 ms (SD 13) ($p < 0.01$). The "effective" diameter calculated from the integrated curves was 7.0 mm (SD 1.1) which is 0.21 mm (SD 0.07) larger than the mean of the systolic and diastolic diameters. The volume blood flow calculated from the integrated curves was 6% higher than that obtained from the mean of the systolic and diastolic diameters. Calculated from the integrated curves, the SV was 5.4 ml (SD 1.6) and $1.8 \text{ ml} \cdot \text{kg}^{-1}$ (SD 0.5). These values were slightly larger than those reported by Tonge et al. (1983). The small difference might be explained by the use of different high-pass filters.

The time relationship of the events of blood velocity and vessel diameter is of importance when calculating volume blood flow. A similar relationship was described by MacDonald (1974) for blood flow and blood pressure in the femoral artery of dog. In future studies this issue should be explored more by studying fetuses at different gestational ages, at different sites of measurement and at different fetal heart rates. The difference in time of these events probably ought to be more pronounced distal to the site of measurement presented, namely in the abdominal aorta close to the bifurcation. The diameter pulse wave (Sindberg Eriksen et al., 1984) travels faster than the blood velocity pulse and the differences might then be more pronounced distally.

C. Fetal blood flow in normal pregnancy

a. Aortic and umbilical volume blood flow (III)

In this longitudinal study on 21 pregnant women, 136 fetal blood flow measurements were performed. The success rate of the measurements upstream in the descending thoracic aorta in fetuses in cephalic presentation, was 100%. Interference with the heart activity could occur in the downstream measurement of blood velocity in the thoracic aorta which was reflected in a lower success rate (83%). The practical difficulty of the downstream measurement in the thoracic aorta was also due to the shape of the maternal abdomen. For the same reason, in the abdominal aorta, were measurements easier to obtain downstream (success rate 90%) than upstream (success rate 88%). Moreover, measuring blood velocity upstream in the fetal abdominal aorta, gas in the maternal intestines sometimes interfered with the ultrasound beam. However, when Doppler signals of good quality were obtained, no difference in the measured blood velocity was found between the two modes of measuring at

any of the three sites. This may also be interpreted as a good momentary reproducibility.

In the thoracic descending aorta, closely grouped velocities were seen on the Doppler spectrum with a frequency shift "window" in the first, high velocity part of the cycle. This indicates a fairly flat flow profile. In the diastolic part, lower and more dispersed velocities were seen than in the first part of the cycle. This pattern is due to a change in the blood flow profile in the parabolic direction.

The time-averaged mean blood velocity did not change with gestational age, giving a mean of $34.6 \text{ (SD } 5.5) \text{ cm} \cdot \text{s}^{-1}$. The diameter increased subsequently with gestational age and correlated with ultrasonically estimated fetal weight ($r = 0.87$). The weight-related cross-sectional area was constant during the last trimester of pregnancy (mean $0.136 \text{ cm}^2 \cdot \text{kg}^{-1}$; SD 0.025). There was a linear increase in the volume blood flow up to the 36th gestational week followed by a flattening. The volume blood flow was correlated to the gestational age ($r = 0.72$). The aortic SV followed nearly the same pattern, except for a small difference due to a decline in FHR by 7.2 % towards term. The decline in the FHR is in accordance with previous reports (Dawes, 1968). The blood flow corrected for the ultrasonically estimated fetal weight was stable till the 36th gestational week, followed by a slight fall. This was also found by Griffin et al. in a cross-sectional study (1983). The mean SV related to the fetal weight was stable ($1.74 \text{ ml} \cdot \text{kg}^{-1}$; SD 0.32). This value is 6% lower than that obtained from the synchronized diameter and velocity curves ($1.8 \text{ ml} \cdot \text{kg}^{-1}$) (II). Study II could not be extrapolated for the whole last trimester and, moreover, it was performed only in a narrow range of FHR and gestational age. Therefore no correction for this factor was performed in study III.

The Doppler shift spectrum in the abdominal aorta revealed a smaller "window" during the high velocity part of the cycle and an even more dispersed spectrum of velocities during the diastolic part of the cycle than in the thoracic part. This indicates a velocity profile which is not as flat as in the thoracic aorta.

The mean blood velocity in the abdominal aorta was stable during the third trimester of pregnancy and did not differ significantly from the velocity in the thoracic part. The time-averaged mean blood velocity was $32.7 \text{ cm} \cdot \text{s}^{-1}$ (SD 5.5). This is consistent with the results found by other groups (Eldridge & Berman, 1983; Erskine & Ritchie, 1985). A linear relation was found between the vessel diameter and the fetal weight ($r = 0.75$). Volume blood flow and SV increased with progress of pregnancy, though not as steeply as in the thoracic aorta. The weight-related cross-sectional vessel area and SV declined slightly with increasing gestational age.

In the umbilical vein the blood flow was continuous and non-pulsating. The time-averaged mean blood velocity was stable throughout the study period (mean $12.6 \text{ cm} \cdot \text{s}^{-1}$; SD 3.1). The diameter of the umbilical vein increased up to the 36th gestational week, followed by a plateau. The weight-related cross-sectional area decreased with the progress of pregnancy ($r = -0.62$). The weight-related blood flow diminished linearly with gestational age, a finding also seen by other groups in cross-sectional studies (Gill et al., 1981; Jouppila & Kirkinen, 1984). There was a highly significant correlation between the umbilical volume blood flow (uncorrected for fetal weight) at the last examination, and placenta weight ($r = 0.83$, $p < 0.001$). The corresponding relation to birth weight was $r = 0.45$ ($p > 0.05$).

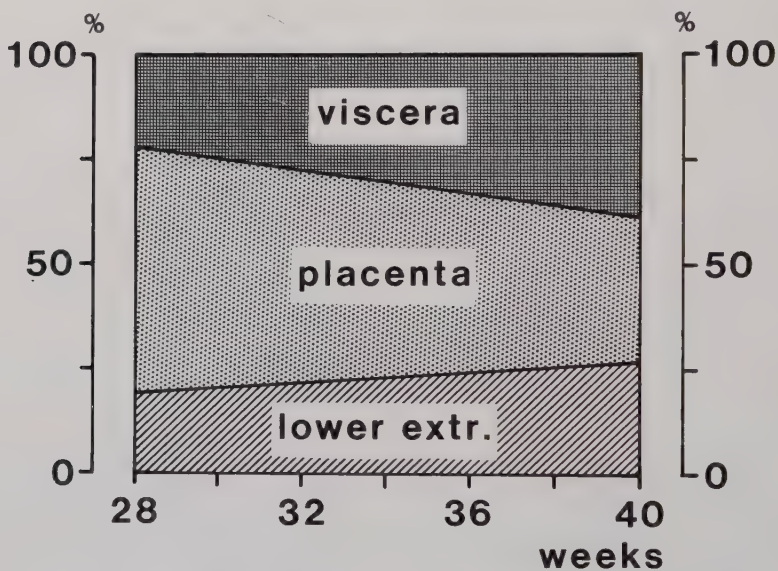


Figure 3. Proportional distribution of the fetal aortic blood flow. The flow in the descending thoracic aorta is defined as 100%.

The blood flow distribution is shown in Fig. 3. The placental proportion of the blood flow in the descending thoracic aorta related to the fetal weight diminished with increasing pregnancy length: in the 28th week, the proportion was 59% and at term 33%. In contrast both the visceral blood flow and the flow to lower extremities increased their proportions from 22 to 39% and from 19 to 28%, respectively. If

the blood flow in the bifurcation level is taken as 100%, the placental proportion decreased from 75 to 54% and the flow proportion to the lower extremities increased from 25 to 46%. The diminishing proportion of the placental flow might be due to the changing ratio of fetal to placental weight with as pregnancy progresses (Gruenewald, 1974). No reports on the distribution of blood flow in the human fetus have been found. Longo et al. (1978) found that 65% of the blood flow in the descending aorta in fetal lambs was directed to the placental vascular bed and 29% to the lower extremities. 77% of the blood flow at the bifurcation level in that study was found to be directed to the placenta and 33% to the lower extremities.

The diameter ratio between the thoracic aorta and the umbilical vein exceeded 1.0 first in the 39th gestational week. As the mean blood velocities in the vessels seem to be relatively constant during the last trimester, it must thus be the changing vessel diameters and their ratios cause the changing distribution of flow.

Only two longitudinal studies on the human fetal aortic blood flow have so far been published (Eldridge & Berman, 1983; Erskine & Ritchie, 1985). Both groups used an ATL duplex scanner (ATL Mark V) which has a sampling volume too small (4 mm diameter and 2 mm depth) for reliable sampling in vessels with dimensions like the fetal aorta (diameter 4 - 8 mm). The ATL uses the sector scanning system which makes it difficult to obtain an optimal insonation angle in the measurements of absolute blood velocities. The average of the maximum Doppler shift was used in those studies to calculate the volume blood flow. The technique for the vessel diameter measurement was also somewhat less precise than in the present technique. In the first study (Eldridge & Berman, 1983) the flow in the abdominal aorta near the bifurcation was measured and found to be higher than the results in the present study, probably due to the above mentioned technical difference.

In the study by Erskine and Ritchie (1985), aortic blood velocity measurements were performed just below the diaphragm. The results in their studies are more like the results in the present study probably due to the fact that the aortic flow profile proximally is closer to flat than distally, which implies a smaller difference between mean and maximum blood velocity. Therefore the overestimation of the volume blood flow using maximum velocity is less pronounced near the fetal heart.

All three studies (Eldridge & Berman, 1983; Erskine & Ritchie, 1985; III) described rather large variations in blood flow. This is obviously due to the sum of the methodological errors and the fetal physiological intra- and interindividual variations.

b. Aortic blood velocity waveform (IV)

The shape of the maximum blood velocity curve differed in the thoracic descending aorta, compared with the abdominal aorta. The peak velocity was higher and the diastolic proportion was lower in the former than in the latter. The lowering of the peak distally is probably due to damping factors, while the increasing diastolic portion probably reflects the nearness to the placental low-resistant vascular bed (Dawes, 1968).

In the thoracic descending aorta, the peak maximum velocity did not change from the 28th gestational week till term (mean $115.6 \text{ cm} \cdot \text{s}^{-1}$; SD 19.0). There was a discrete increase in the minimum velocity with the increasing gestational age ($r = 0.23$) (mean $16.8 \text{ cm} \cdot \text{s}^{-1}$; SD 4.9). The PI and the RS during the last trimester had means 1.96 (SD 0.31) and 29.9 (SD 4.9) respectively, and coefficients of correlation to the gestational age of $r = 0.15$ and $r = -0.22$, respectively. The RS had coefficients of correlation to the acceleration time and peak velocity of $r = 0.49$ and $r = 0.52$ respectively. Acceleration time and percentage acceleration time increased slightly as pregnancy progressed ($r = 0.45$ and $r = 0.43$, respectively). Neither these parameters nor PI and RS were strongly related to FHR. The DS was constant during the last trimester and related to PI ($r = 0.72$).

In the abdominal aorta, the peak velocity (mean $99.7 \text{ cm} \cdot \text{s}^{-1}$; SD 18.8) and the PI (mean 1.68; SD 0.28) were stable during the third trimester. The minimum velocity (mean $18.6 \text{ cm} \cdot \text{s}^{-1}$; SD 5.7) increased slightly with increasing gestational age ($r = 0.28$). The RS and the DS showed a slight tendency to decline towards term ($r = -0.21$ and $r = -0.25$, respectively).

Several authors found changes of the blood velocity waveform in the umbilical arteries indicating lowering of the peripheral vascular resistance with increasing gestational age in cross-sectional studies (Fitzgerald & Drumm, 1977; McCallum et al., 1978; Stuart et al., 1980) and one longitudinal study (Reuwer et al., 1984). Different parameters have been used for the evaluation of peripheral vascular resistance in the placental bed, e.g. the A/B-ratio (peak to minimum blood velocity) (Stuart et al., 1980; Giles et al., 1982) and the PI (Reuwer et al., 1984). Giles et al. (1985) demonstrated a close correlation of the A/B ratio obtained by the continuous wave and by the pulsed wave Doppler technique. Lowering of the indices of peripheral vascular resistance was not found in the fetal descending aorta (IV). This is probably due to the changing distribution of flow with gestational age. As described above, the proportion of the aortic blood flow to the high - resistant peripheral

circulation increased towards term.

Early changes in the blood velocity waveform recorded from the fetal descending aorta in cases of fetal hypoxia were found by Jouppila and Kirkinen (1984). They used mean blood velocity for waveform analysis, as did Wladimiroff et al. (1983). Griffin et al. (1983) characterized the blood velocity waveform by a so-called frequency index profile, using maximum blood velocity for the analysis. The maximum blood velocity is used in the present study (IV), as it is less sensitive for certain important sources of error, e.g. interference from nearby vessels. It is also less sensitive for various blood flow profiles than is the mean aortic blood velocity. Furthermore in a situation of fetal compromise, e.g. in progressing fetal hypoxia, the mean velocity will be influenced by the high-pass filters earlier than the maximum velocity.

D. Fetal heart arrhythmia

a. Haemodynamic assessment (V)

Three non-invasive methods were applied for diagnosis and evaluation of fetal heart arrhythmia in 2 cases. In the first fetus, irregular fetal heart sounds with periods of tachycardia ($> 200 \text{ beats} \cdot \text{min}^{-1}$) and bradycardia ($85\text{-}90 \text{ beats} \cdot \text{min}^{-1}$) were heard in the 25th gestational week. Thereafter, periods of regular rhythm and periods of frequent supraventricular extrasystoles were found. In the 33rd gestational week, fetal phonocardiography revealed a short systolic murmur in the 50 Hz frequency band during periods of beats grouped in pairs.

Ultrasonic measurement of the fetal aortic blood flow showed that the peak maximum velocity was related to the length of the preceding beat-to-beat interval. The peak maximum velocity after a prolonged beat-to-beat interval was significantly higher than that during periods of tachycardia. As the peak maximum blood velocity is related to the stroke volume (Hatle & Angelsen, 1981), the present finding supports the validity of the Frank-Starling law in the human fetus as suggested by Marsál and Eik-Nes (1980).

During the periods of paired beats, the spectrum analysis of the aortic blood velocity revealed an additional spike in the second beat preceding the peak velocity. The spike coincided in time with the murmur seen on the phonocardiographic recordings and was present only during this specific type of arrhythmia. Simultaneous abdominal fetal ECG showed a broader QRS complex in the second

beat than in the first beat of each couple. These findings might indicate bundle-branch blocked supraventricular extrasystoles with a changed pattern of myocardial contraction.

In the second case, fetal bradycardia with a frequency of $56 \text{ beats} \cdot \text{min}^{-1}$ was heard in the 25th gestational week. A fetal phonocardiogram revealed varying amplitude of the first heart tone, similar to a finding seen in adults in cases of AV-block. The phenomenon is called *bruit de canon* and is due to ventricular contractions at varying degrees of closure of the atrioventricular valves (Strandell, 1967). In the present case, fetal blood flow measurements were performed during the pregnancy, revealing volume blood flow in the descending aorta and in the umbilical vein within the normal range. The blood velocity recording in the descending aorta showed beats with a frequency of $56 \text{ beats} \cdot \text{min}^{-1}$. On the blood velocity traces from the IVC, pulsations were seen appearing as deflecting velocities with a frequency of $126 \text{ beats} \cdot \text{min}^{-1}$.

The usefulness of abdominal fetal ECG was demonstrated; in the first case the form of the QRS complex aroused suspicion of bundle-branch blocked extrasystolic beats. The fetal phonocardiogram is sometimes difficult to evaluate, but gave additional information concerning rhythm regularity, and closure and opening of the atrioventricular valves. The abdominal fetal ECG and phonocardiogram can with advantage be used simultaneously, which might facilitate interpretation of the traces. The combined real-time and pulsed Doppler technique gave information on the volume blood flow and on the short-term compensatory mechanisms of the beats following extrasystoles. It also made possible a more reliable diagnosis of the type of arrhythmia, as the atrial activity was reflected in the traces from the IVC, whereas the ventricular activity was seen in the traces from the fetal descending aorta. This demonstrated the dissociated atrial and ventricular activity, although the traces could not be obtained simultaneously.

b. Circulatory effects and compensatory mechanisms of fetal cardiac arrhythmia (VI)

Supraventricular arrhythmia

Fetuses with heart arrhythmia constitute a group which can be seen as a model for the investigation of the physiology of fetal circulation. The circulatory compensation mechanisms in fetal heart arrhythmia supported the validity of the Frank-Starling's law for the human fetal heart. In 20 fetuses after a pause following supraventricular extrasystoles, significantly higher ($p < 0.001$) maximum peak velocities were found ($123.0 \text{ cm} \cdot \text{s}^{-1}$, SD 22.5) than those during periods of regular rhythm in the same fetuses ($107.1 \text{ cm} \cdot \text{s}^{-1}$, SD 20.4) and than of the extrasystole ($76.8 \text{ cm} \cdot \text{s}^{-1}$, SD 25.2).

The same relationship was seen in the corresponding beats for the RS (27.9, SD 6.9; 23.1, SD 8.1 and 21.3, SD 10.7, respectively) and for the acceleration (1519, SD 447; 1305, SD 434 and 695, SD 339 $\text{cm} \cdot \text{s}^{-2}$, respectively). No differences were found in the acceleration percentage time between the various types of beats. Significant correlations were found in the extrasystolic and the postextrasystolic beats between the preceding beat-to-beat interval and the peak velocity ($r=0.67, p < 0.001$), the RS ($r=0.60, p < 0.001$) and the systolic acceleration ($r=0.51, p < 0.05$). The time-averaged mean blood velocity ($32.0 \text{ cm} \cdot \text{s}^{-1}$, SD 4.8) and the aortic volume blood flow ($249.6 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) did not differ from normal values. The waveform and the volume blood flow were not changed in 2 fetuses with severe cardiac malformations.

An increased beat-to-beat interval enables augmented ventricular filling which stretches the myocardial fibres and increases myocard contractility. Marsál et al. (1980) showed for the first time the relationship between the preceding beat-to-beat interval and the peak velocity in the human fetus. In experimental studies on fetal sheep, the RS was significantly related to the left ventricular dP/dt as long as PI, reflecting mainly the peripheral vascular resistance, remained constant (Maršál et al., 1985). Changes in the peripheral resistance can hardly appear during one single extrasystole. Peak velocity, RS, and acceleration were significantly correlated to the ventricular filling time in the present study (VI), suggesting strongly that these parameters reflect heart muscle contractility also in the human fetus.

The RS is independent of the insonation angle, which increases its reliability in practical use. When the preceding beat -to-beat interval was tested against the RS and peak velocity over longer periods of regular rhythm within the normal frequency range, no significant correlation was found. This might be due to the influence of factors other than the ventricular filling time, e.g. the vagal tone and the level of catecholamines.

In 3 fetuses extrasystoles in trigeminy were found. Blood velocity traces in the IVC reflected atrial contractions corresponding to dropouts of aortic beats. The aortic beats appeared coupled in pairs. The peak aortic velocity was higher in the first postextrasystolic beat than in the second coupled beat.

Six fetuses had missed beats also defined as sinus arrest, as there was a loss of atrial contractions in the IVC. The first postpausal beat had a higher peak velocity than the other beats ($p < 0.05$). No other significant differences were seen in the waveform parameters or volume blood flow.

Four fetuses had supraventricular tachycardia with aortic frequencies of 200 - 238 beats $\cdot$ min⁻¹. Mean peak velocity, RS, and acceleration were lower in all 4 cases compared with the normal material as was the averaged stroke volume (0.96 ml $\cdot$ kg⁻¹, SD 0.09). The acceleration time percentage was higher (26.9 %) although the acceleration time was lower (74 ms) than in the normal material. The volume blood flow was normal.

Atrioventricular block

In 5 cases of atrioventricular block, total dissociation between the atrial and ventricular contractions was reflected as pulsations in the IVC and the aorta of different frequencies. One of these fetuses which had a large ventricular septum defect, ascites and hydrothorax seen *in utero* died. Blood flow measurement in the thoracic descending aorta 12 hours prior to death revealed low mean blood velocity (11.3 cm $\cdot$ s⁻¹) and low volume blood flow (77 ml $\cdot$ min⁻¹ $\cdot$ kg⁻¹). RS and acceleration were high (68.8 and 1458.6 cm $\cdot$ s⁻¹, respectively). This dying fetus had thus signs of fetal heart failure indicating that factors other than ventricular filling can affect cardiac function, e.g. the coexistence of fetal heart malformation.

The other 4 fetuses with AV-block had higher peak velocity (127.6 cm $\cdot$ s⁻¹, SD 5.0), RS (44.7, SD 7.7) and acceleration (1638 cm $\cdot$ s⁻², SD 406), longer acceleration time (92.7 ms) but shorter acceleration time percentage (10.3%, SD 2.8) than normally. Mean aortic blood velocity and flow were within normal range. The averaged stroke volume was increased (mean 3.57 ml $\cdot$ kg⁻¹, SD 0.59) probably due to the increased ventricular filling and the increased myocardial contractility. This is supported by the finding of the increased RS and the acceleration.

Ventricular arrhythmia

Ventricular extrasystoles were found in 3 fetuses. There was no consistent pattern in the waveform parameters, probably due to the character of this arrhythmia with varying haemodynamic efficiency.

In the total material of fetuses with severe cardiac arrhythmia, 6 had severe cardiac malformations. Only one dying fetus showed aberrant blood velocity waveform, low volume blood flow and signs of cardiac insufficiency. This demonstrates the ability of the fetal heart to maintain adequate circulation despite a severe arrhythmia and malformation. Tonge et al. (1984) demonstrated decreasing SV at FHR below 50 beat $\cdot$ min⁻¹ and above 250 beats $\cdot$ min⁻¹, which probably represents the range of Frank-Starling's law. No case in the present material had FHR outside this range.

c. Clinical outcome of fetuses with cardiac arrhythmia (VII)

Of 113 cases of fetal heart arrhythmia, there 94 were cases of supraventricular origin, 5 with AV-block and 14 with ventricular extrasystoles.

Supraventricular arrhythmia

Supraventricular extrasystoles were found in 84 fetuses. Two fetuses died *in utero* due to placental abruption and one infant died due to muscular dystrophy at the age of 6 months. One neonate from this group had a trisomy 18 and a ventricular septum defect.

Four of the 6 fetuses with paroxysmal supraventricular tachycardia had no intrauterine signs of cardiac insufficiency at real-time ultrasound examination. Two fetuses had heart enlargement and were treated with digoxin *in utero*. The treatment resulted in conversion to regular rhythm with normal FHR. In 2 fetuses the tachycardia converted spontaneously *in utero* and in the 2 remaining fetuses the tachycardia persisted during labour and after birth. The latter two neonates were treated with digoxin and propranolol after which the tachycardia regularized. None of the 6 fetuses in this group had congenital cardiac malformations.

One fetus had an atrial flutter with a frequency of 360 - 380 atrial contractions per min and aortic pulses with a frequency of 190 beats $\cdot$ min⁻¹ in the 37th gestational week. Real-time ultrasound examination revealed slight ascites. Intrauterine digoxin treatment was initiated and the flutter converted to normal rhythm within 3 days, when the ascites also had vanished. The flutter reoccurred after 5 days of regular rhythm and the child was therefore delivered by means of cesarean section. Additional digoxin treatment after birth regularized the rhythm again. This baby was otherwise healthy.

Sinus bradycardia was found in 3 fetuses with heart frequencies of 95-110 beats $\cdot$ min⁻¹. All 3 were born vaginally; 2 were healthy and one neonate died within one week of a cardiomyopathy with lipid infiltration of the myocardium and agenesis of corpus callosum.

Atrioventricular block

AV-block was diagnosed in 5 fetuses. Two had grade II AV-block which in both cases converted to normal rhythm. In one of these remained the heart rhythm normal and the neonate was healthy. In the other case the AV-block reoccurred immediately after birth, this time as a grade III AV-block. This neonate had a severe cardiac malformation and died of cardiac insufficiency after one month. The remaining 3

fetuses had grade III AV-block *in utero* . One of them died *in utero* of cardiac insufficiency (ascites, hydrothorax, heart enlargement); that fetus had a large ventricular septum defect and a phenotype like trisomia 21.

In one fetus the AV-block was diagnosed in the 33rd gestational week. This fetus showed signs of cardiac insufficiency with ultrasonically diagnosed ascites and hydrothorax and a cardiac malformation (consisting of a large atrial septum defect and an aberrant entering of the superior vena cava) on which it was difficult to judge the operability. With this background a digoxin treatment was initiated *in utero* . The signs of cardiac failure disappeared and a well circulatory compensated child was born vaginally after spontaneous labour in the 37th gestational week. Cardiac investigation postpartum revealed an inoperable heart malformation and the child died at the age of one week after the medication was terminated. The autopsy revealed a common atrioventricular foramen , hypoplastic left ventricle and aberrant inlet of the superior vena cava. The third fetus, with grade III AV-block but no signs of heart failure *in utero* , was born at term. The baby showed no signs of cardiac insufficiency or cardiac malformation postpartum.

Ventricular arrhythmia

Fourteen fetuses had ventricular extrasystole. None of them had any cardiac malformation. One fetus was growth-retarded and 4 were distressed in labour; the postnatal course was uneventful. Two of the pregnant women had pre-eclampsia.

In two published studies on large materials of fetal heart arrhythmia, extrasystoles were considered as a "benign" finding not connected with fetal complications (Kleinman et al., 1983; Komáromy et al., 1977). However, in the present study, fetuses with supraventricular extrasystoles were afflicted with an increased frequency of distress in labour and of cardiac diseases. The existence of fetal cardiac disease in this group was also reported by Stewart et al. (1983) and Wladimiroff et al. (1984).

It is generally accepted that fetal supraventricular tachycardia can result in fetal cardiac failure and fetal complications (Schreiner et al., 1978; Kleinman et al., 1983; Komáromy et al., 1977; Valerius & Jacobsen 1978; Stewart et al., 1983). An increased frequency of cardiac malformations was seen in the present material in fetuses with AV-blocks, as was also claimed by others (Komáromy et al., 1977). Compared with the general population, the present total material had a significantly higher perinatal mortality (3.5% vs 0.7%; $p < 0.001$), higher neonatal (8-28 days) mortality (1.8% vs 0.1%, $p < 0.001$), higher frequency of congenital malformations (6.2% vs 2.0% ; $p < 0.01$) and of fetal distress in labour (28.3% vs 13.5%; $p < 0.001$).

d. Intrauterine treatment of supraventricular paroxysmal tachycardia (VIII)

A case of irregular fetal heart sounds was found in the 29th gestational week in an otherwise normal pregnancy of a 25-year-old healthy woman. The fetal cardiogram revealed a frequency of $140 \text{ beats} \cdot \text{min}^{-1}$ with normal variability. Fetal abdominal ECG showed a cardiac frequency of $300\text{--}400 \text{ beats} \cdot \text{min}^{-1}$. Real-time linear array ultrasound examination showed a marked heart enlargement and atrioventricular valves moving irregularly. Due to the severe fetal arrhythmia and signs of imminent cardiac insufficiency in early third trimester pregnancy, digoxin treatment of the fetus *in utero* was initiated. On the first day of treatment, 0.25 mg digoxin (Digoxin^R ACO) was twice administered intravenously to the mother. The therapy was maintained by giving 0.25 mg orally each day. After 24 hours the rhythm regularized and the heart size normalized. The oral therapy was continued until delivery and the fetal arrhythmia did not recur. No cardiac malformations were found at ultrasound examination *in utero*, the normal heart anatomy being confirmed after birth. After 38 gestational weeks the woman gave birth vaginally after spontaneous labour to a healthy girl weighing 3050 g with Apgar score 8 at 5 min and 9 at 10 min.

The simultaneous digoxin concentrations ($\text{nmol} \cdot \text{l}^{-1}$) in fetal and in maternal compartments were: amniotic fluid/maternal serum, 1.1/1.6; scalp blood sample/maternal serum, 0.9/1.6; umbilical vein/maternal serum, 1.0/1.1 and umbilical artery/maternal serum, 0.9/1.1.

Saarikoski (1976) and Rogers (1972) had reported on the passage of digoxin over the placenta barrier. Intrauterine digoxin treatment of fetal cardiac failure had previously been suggested (Valerius & Jacobsen, 1978) though it had not succeeded hitherto (Newburger & Keane, 1979). Since the publication of the present paper (VIII), several reports on the varying success of intrauterine digoxin treatment have been published (Kerenyi et al., 1980; Harrigan et al., 1981; Stewart et al., 1983). The varying therapeutic effects of intrauterine treatment might be due the individual sensibility to the digoxin but also to suboptimal concentration. Recently, Graves et al. (1984) suggested individual calculation of the loading and maintenance digoxin dosis, taking into account the maternal body weight and the creatinine clearance.

Summary

The ultrasonic method combining real-time linear array and pulsed Doppler ultrasound technique for measurement of fetal blood flow was tested in an experimental study on pigs. Simultaneous measurements of the aortic blood flow were performed by means of the ultrasound technique and an EM method. The experiment animals (domestic pigs) had the same HR range and size of abdominal aorta as the human fetus in late pregnancy. The study revealed highly significant correlations between the results obtained by the two methods (r within range 0.89-0.98) indicating good accuracy of the combined ultrasound technique, in the hands of experienced operators aware of possible sources of error.

In an attempt to circumvent the impossibility of using real-time and Doppler ultrasound simultaneously, subsequent registrations in the descending thoracic aorta of 10 term human fetuses were performed on the pulsatile diameter vessel changes by means of an ultrasonic echo-tracker and of the mean blood velocity with pulsed Doppler ultrasound technique. The curves were synchronized by abdominal fetal ECG, analysed, and integrated by means of a digitizer and a microcomputer, and the volume blood flow was calculated. The peak mean velocity preceded the maximum systolic diameter by 37 ms. An "effective" diameter was determined from the flow values based on the synchronized curves. When using the "effective" diameter, the calculated volume blood flow was 6% greater than that calculated from the mean of the systolic and diastolic diameters. The aortic stroke volume was 5.4 ml ($1.8 \text{ ml} \cdot \text{kg}^{-1}$). The study gives interesting new information on fetal circulatory physiology, though, is the method too complicated for clinical use.

Twenty-one fetuses of healthy women with normal pregnancies were examined longitudinally in the last trimester of pregnancy. Mean blood velocity in the fetal descending aorta was stable from the 27th gestational week till term, in both the thoracic part measured upstream ($34.6 \text{ cm} \cdot \text{s}^{-1}$) and in the abdominal part measured downstream ($32.7 \text{ cm} \cdot \text{s}^{-1}$). There were no significant differences between the two sites. Constant mean blood velocity was also found in the intraabdominal part of the umbilical vein ($12.6 \text{ cm} \cdot \text{s}^{-1}$) during the period.

Blood velocity did not differ when measured upstream vs. downstream at any of the three sites. This is important in a methodological respect, but also as a test of immediate reproducibility. In cephalic presentation, velocity measurement upstream was obtained in 100% in the thoracic aorta and in 90% measured downstream in the abdominal aorta. In these directions it was easiest to perform measurements due to the

shape of the pregnant abdomen. The diameter of the fetal thoracic aorta was growing linearly during the third trimester; the ratio of the vessel cross-sectional area and the ultrasonically estimated fetal weight was constant ($0.136 \text{ cm}^2 \cdot \text{kg}^{-1}$). The growth in the diameter of the abdominal aorta was also linear, but not as steep; the ratio of the cross-sectional area to the fetal weight declined therefore with progress of pregnancy.

Volume blood flow per kg fetal weight in the descending thoracic aorta was fairly stable, while the flow in the umbilical vein decreased with gestational age. The proportion of flow to the lower extremities and to the visceral vascular bed increased, while the placental proportion decreased. As the blood velocities were constant, the change in the distribution of blood flow was due to the different patterns of growth of the vessel diameters at various sites.

The study of the maximum blood velocity waveform in normal pregnancy revealed higher peak blood velocity and lower diastolic velocity in the thoracic descending aorta ($115.6 \text{ cm} \cdot \text{s}^{-1}$ and $16.8 \text{ cm} \cdot \text{s}^{-1}$, respectively) than in the abdominal aorta (99.7 and $18.6 \text{ cm} \cdot \text{s}^{-1}$, respectively) which reflects the effect of an increased distance from the fetal heart and also the lower peripheral resistance in the abdominal aorta close to the placental circulation. The aortic stroke volume was $1.74 \text{ ml} \cdot \text{kg}^{-1}$ in the thoracic part and did not change during the study period.

The peak aortic blood velocity was fairly constant during the third trimester and the minimum diastolic velocity increased slightly at the two sites of measurement with progress of pregnancy. The PI and the RS were constant in the thoracic aorta (1.96 and 29.9, respectively) and higher than in the abdominal aorta (1.68 and 25.7, respectively). The RS and the DS declined slightly with increasing gestational age at the latter site of measurement. The DS was stable in the thoracic aorta (5.3).

Three non-invasive methods were applied to diagnose human fetal arrhythmia, namely abdominal ECG, phonocardiography and combined real-time and pulsed Doppler ultrasound technique. Fetal ECG gave information on the type of arrhythmia; the phonocardiogram revealed heart murmurs and in one case of AV-block a phenomenon similar to *bruit de canon*. The ultrasound technique for blood flow measurements showed an increased peak maximum velocity after a compensatory pause thus supporting the validity of the Frank-Starling's law for the human fetus. The etiology of the pulsatile pattern of the IVC blood flow was ascribed to atrial contractions. This was based on the finding of total dissociation of the aortic beats and the pulsations in the IVC in a case of fetal grade III AV-block.

Fetal heart arrhythmia can be considered to be a model for the study of human fetal cardiovascular physiology by means of the combined real-time and pulsed Doppler ultrasound technique. The atrial contractions are reflected in the IVC blood flow during fetal apnea, making it possible to differentiate atrial premature beats from extrasystoles of ventricular origin. Peak velocity, RS and acceleration were lower in cases of fetal supraventricular tachycardia than in fetuses with normal rhythm; corresponding values in cases with atrioventricular block were higher than normal. In fetuses with cardiac arrhythmia with or without structural malformations, measurement of the aortic volume flow give information on imminent cardiac failure. Of the 37 fetuses with various types of cardiac arrhythmia, only one dying fetus with a large ventricular septum defect and a grade III AV-block had mean aortic blood velocity and flow below the normal limits. The other 5 fetuses with cardiac malformations had normal aortic blood velocity and flow. This demonstrates the considerable ability of the human fetal heart to maintain an adequate circulation despite a severe cardiac malformation.

113 cases of fetal cardiac arrhythmia were diagnosed and classified *in utero* and the clinical outcome of pregnancy was studied. 94 fetuses had a supraventricular arrhythmia, 5 had AV-block and 14 had ventricular arrhythmia. Overall there was significantly increased frequency of congenital malformations (6.2%), fetal distress (28.3%), perinatal mortality (3.5%), neonatal (8-28 days) mortality (1.8%) compared with the general population. Three fetuses were successfully treated *in utero* with digoxin for cardiac failure caused by supraventricular tachycardia (2 cases) and by grade III AV-block (one case). Cardiac malformations were found in the supraventricular arrhythmia group (2 out of 94) but the highest frequency was found in the AV-block group (3 out of 5).

Finally, a case report is given on the first published successful digoxin treatment *in utero* of a 29-week-old fetus with supraventricular paroxysmal tachycardia and ultrasonic signs of fetal heart failure. The fetus showed concomitant ultrasonic signs of fetal heart failure. Digoxin treatment *in utero* resulted in conversion of the tachycardia to normal and disappearance of the signs of fetal heart failure. Digoxin concentrations in fetal compartments were found to be somewhat lower than the maternal concentrations.

Conclusions

A non-invasive ultrasound method for fetal blood flow measurement combining real-time linear array and 2 MHz pulsed Doppler technique was tested against the invasive electromagnetic method in an animal model; good agreement between the results obtained by the two methods was found.

In human fetus in late pregnancy, the peak velocity of blood flow in the thoracic descending aorta preceded the maximum systolic diameter. Taking this into account when calculating volume blood flow resulted in a 6% higher value than if this was disregarded.

The aortic blood flow was studied in a longitudinal study on human normal fetuses. Mean blood velocity in the fetal descending thoracic and abdominal aorta was stable during the third trimester of normal pregnancy, while the corresponding vessel diameters increased linearly with gestational age. Volume blood flow corrected for ultrasonically estimated fetal weight decreased mainly in the umbilical vein. The placental proportion of the blood flow in the descending thoracic aorta diminished with progress of pregnancy, while the proportion of flow to viscera and lower extremities increased.

The waveform parameters of the fetal aortic maximum blood velocity were relatively stable during last trimester. The peak velocity was higher and the minimum velocity lower in the fetal descending thoracic aorta than in the abdominal aorta.

Abdominal fetal ECG, fetal phonocardiography and combined real-time and pulsed Doppler technique are important non-invasive tools for diagnosing and assessing the circulatory effects of fetal heart arrhythmias. Indications for the validity of the Frank-Starling's law were shown by the combined ultrasound method. Recordings of the blood velocity in the descending aorta and the inferior vena cava enabled typing of fetal heart arrhythmias according to their origin, as the ventricular activity is reflected in the aorta and the atrial activity in the inferior vena cava.

Important information on the physiological compensatory mechanisms of the fetal heart was obtained by using the combined real-time and pulsed Doppler technique on a large material of fetal heart arrhythmias, which could be seen as an experimental model in this respect. The validity of the Frank-Starling's law was supported as was the opinion that the rising slope (RS) of the blood velocity in systole reflects myocardial contractility. In most cases the blood circulation could be maintained within normal limits despite a serious fetal heart malformation.

Increased frequencies of pregnancy complications, fetal distress, perinatal and neonatal mortality and fetal malformations were found in a large material of fetal heart arrhythmias. Four fetuses with severe cardiac arrhythmia were successfully treated *in utero* . Fetal heart malformations were found mainly in the group with atrioventricular block but also in the group of supraventricular arrhythmia.

Treatment of fetal supraventricular paroxysmal tachycardia in utero by digoxin administration to the mother is possible.

If done with care, measuring of fetal blood flow in the descending aorta and the umbilical vein and performing velocity waveform analysis of the fetal aortic blood velocity seem to be valuable in the study of the normal human fetal physiology and the development of circulation, in the evaluation of cardiac performance and peripheral vascular resistance.

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COMPARISON OF BLOOD FLOW MEASUREMENTS BY REAL-TIME/DOPPLER ULTRASOUND
AND ELECTROMAGNETIC FLOWMETER

Eik-Nes, S.H.*, Grip, A.**, Kristoffersen, K.**, Lingman, G.+, Maršál,
K.+, Vernersson, E.++

* Department of Obstetrics and Gynecology, ** Department of Biomedical
Engineering, University Hospital, Trondheim, Norway

+ Department of Obstetrics and Gynecology, ++ Department of Experimen-
tal Surgery, University Hospital, Malmö, Sweden

ABSTRACT

A method employing the combination of Doppler and real-time ultrasound was compared with an acknowledged electromagnetic method of quantitating blood flow in the abdominal aorta of three pigs. A laparotomy was performed and the aorta of the animals dissected free. Variations in the aortic blood flow were achieved pharmacologically. A total of 96 simultaneous recordings were performed on the animals with a blood flow range from $60 \text{ ml} \cdot \text{min}^{-1}$ to $1,400 \text{ ml} \cdot \text{min}^{-1}$. The correlation coefficient between the two methods ranged from 0.89 to 0.98 and the results were linear over the full range of observation. On average the ultrasound method estimated 12.1% higher than the electromagnetic method, a systematic error most of which could be explained as caused by the highpass filter of the ultrasound method. The results were not influenced by the heart rate, mean blood velocity or aortic diameter. The study concludes that the combined pulsed Doppler technique, which was originally designed to measure fetal blood flow, provides results which are in agreement with the electromagnetic method when used under experimental conditions.

INTRODUCTION

The recent development of advanced ultrasound techniques made possible studies of the blood flow in the human fetal umbilical vein (1). Later a method for noninvasive quantitative assessment of both the arterial and venous blood flow in the human fetus was developed using a combined real-time and pulsed Doppler ultrasound technique (2,3). The latter method for Doppler measurement of blood flow has been extensively used for quantification of the blood flow in the fetus (4,5,6) and has shown potential in the noninvasive evaluation of the hemodynamic condition of the human fetus. Angelsen and Brubakk (7) evaluated the reliability of the pulsed Doppler technique against true flow in an in vitro setup. So far, no in vivo or in vivo-like comparison has been made of this real-time linear array and pulsed Doppler technique with other established blood flow measuring techniques.

The purpose of this study was to evaluate the noninvasive Doppler and real-time technique against an accepted electromagnetic method for blood flow measurement in an animal model.

MATERIAL AND METHODS

Ultrasound methods

The method for blood flow measurement employed the combination of a multilinear ultrasound real-time scanner for fetal vessel imaging (ADR model 2130, Advanced Diagnostic Research Corp., Tempe, Arizona) and a pulsed Doppler instrument for measurement of blood velocity (ALFRED, Vingmed A/S, Oslo, Norway). The real-time scanner was calibrated to the velocity of sound $1540 \text{ m}\cdot\text{s}^{-1}$, with a 3.5 MHz transducer. The Doppler instrument was used in the 2 MHz pulsed mode with the high-pass filter cut-off frequency set at 100 Hz. The unfocused Doppler transducer had a diameter of 10 mm. In the 2 MHz mode the sample volume at a depth of 6-10 cm has an approximated length and diameter of 10 mm. The Doppler instrument produced analogue output signals of the maximum and mean instant blood velocity, and the mean velocity averaged over a period of three seconds. In addition, the Doppler

audio signals were monitored continuously. The Doppler instrument was calibrated according to internal signals corresponding to the velocities 0.1, 0.2, 0.5 1.0 and 2.0 $\text{m}\cdot\text{s}^{-1}$. The Doppler transducer was attached to the real-time transducer at a fixed angle of 45° as shown in Fig. 1. Thus, when the real-time transducer was kept parallel to the vessel of interest, the angle between the Doppler beam and the vessel was known (45°). To avoid interference between the imaging and the Doppler ultrasound, a toggle switch was used to turn the transmitter of one instrument off and the other on. A spectral analyzer (DAISY, Vingmed A/S, Oslo, Norway) was also included in the set-up to make on-line visual evaluation of the Doppler spectra possible.

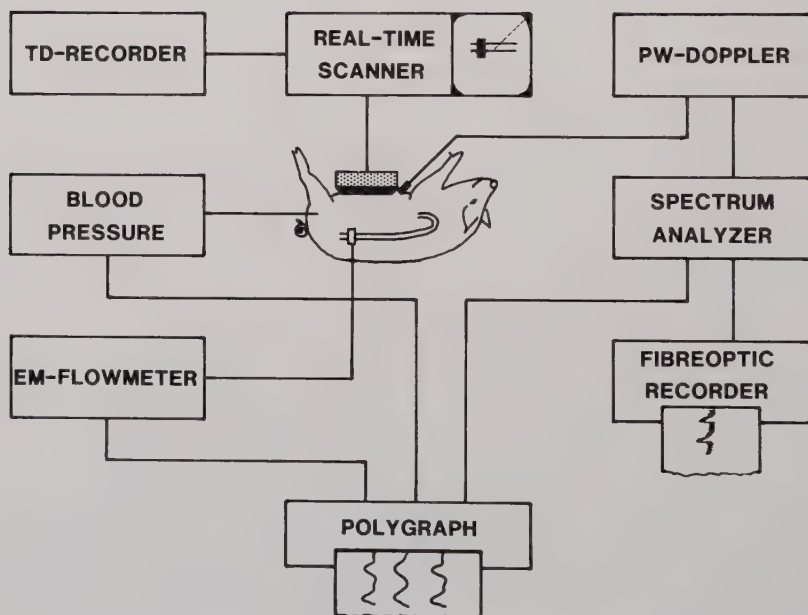


Figure 1. Block scheme of the experimental set-up for the simultaneous blood flow measurements in pig's aorta by pulsed-wave Doppler (PW-Doppler) and electromagnetic (EM-flowmeter) techniques.

The diameter of the vessel was measured from the outer to the inner border of a longitudinal section of the vessel walls as seen on the B-mode ultrasound image. The diameter measurements were made by a Time-Distance-recorder (TD-recorder) (8) which was coupled to the real-time scanner. The calipers of the TD-recorder worked in 0.4 mm steps. The final vessel diameter was calculated as the mean of ten measurements on ten different frozen images.

The blood flow was calculated according to the formula:

$$Q = \frac{V \cdot d^2 \cdot \pi \cdot 60}{4 \cdot \cos \alpha}$$

where V is the time-averaged mean blood velocity, d is the diameter of the vessel and α is the angle of insonation (45°). The blood flow was expressed in $\text{ml} \cdot \text{min}^{-1}$.

Electromagnetic method

The Blood Flow Meter 376 (Nycotron A/S, Drammen, Norway) was used. Transducers with various internal diameters were available, so that the transducer always adapted to the vessel walls. The output signals of the electromagnetic flowmeter included the analogue signals of the instant flow and its integral. A built-in electronic integrator displayed digitally the absolute amount of blood flow. The transducers were first calibrated in vitro mounted on tubes flushed with saline. Additionally, the employed transducers were calibrated in vivo by clamping the abdominal aorta 20 cm upstream from the transducer and infusing 500 cc of the animal's own blood drawn from a jugular vein. Zero flow level for calibration was assured by clamping the vessel upstream from the transducer.

Preparation of the animal

The experiments were performed on five healthy domestic pigs each weighing 22-25 kg. Two pigs were used to establish the operative technique and the measurement procedure. Three pigs were used to compare the two blood flow measuring techniques.

An indwelling intravenous cannula was introduced to the external jugular vein and anesthesia was induced by thiopentone sodium $20 \text{ ml} \cdot \text{kg}^{-1}$ (Pentothal^R, Abbott). The pigs were intubated and ventilated with 70% nitrous oxide in oxygen. Further increments of Pentothal (50-100 mg/dose) and fenatyl (Leptanal^R, Leo) (0.2 mg/dose) were given subsequently during preparation and flow measurements to maintain the narcosis.

Operative procedure

A midline laparotomy was made and the intestines of the animal from the duodenum to the sigmoid colon were removed. The abdominal aorta was then dissected free below the departure of the renal arteries to the bifurcation and all the branches were ligated. An intraarterial pressure transducer was inserted in the femoral artery. The pigs were supplied with a catheter a de meure and a heating blanket was placed under the pig to maintain the body temperature. The abdominal cavity was filled with saline solution at body temperature.

Induction of blood changes

Variations in the aortic blood flow were achieved pharmacologically. The flow was increased by rapid infusion of 0.5 l dextran 70 (Macrodex^R, Pharmacia). After reaching the maximum, the blood flow was gradually allowed to decrease to the preinfusion value. Low aortic blood flow was obtained after injecting 5-10 IU vasopressin intravenously (Postacton^R, Ferring AB); thereafter the flow gradually restituted itself. Intravenous injections of Atropin 0,5 mg and propranolol 1 mg (Inderal^R, ICI) caused changes of the heart rate with minimum changes of the aortic blood flow.

Comparative recording of the aortic blood flow

An electromagnetic transducer of appropriate size was mounted on the aorta cranial to the bifurcation. The ultrasound transducer was manually kept parallel to the aorta and at a distance of approximately 8-10 cm. The sample volume of the Doppler instrument was placed 3 cm proximal to the electromagnetic transducer. In rapid progression the

diameter of the vessel was measured five times with the TD-recorder, then a simultaneous registration of the blood flow with the Doppler and electromagnetic technique was made after which the diameter was measured another five times. The final diameter to be used for that particular recording was then calculated as the mean of those ten measurements. On a polygraph (Recomed 330-P Hellige, Freiburg, Germany) the maximum, mean and time-averaged blood velocity signals from the Doppler flowmeter were recorded along with the signals of the electromagnetically measured blood flow, the integral thereof and the arterial pressure (Fig. 1).

RESULTS

A total of 96 simultaneous measurements were performed on three pigs; 18, 21, and 57 on each pig, respectively. The blood flow range was between $60 \text{ ml} \cdot \text{min}^{-1}$ and $1,400 \text{ ml} \cdot \text{min}^{-1}$ and the heart rate range

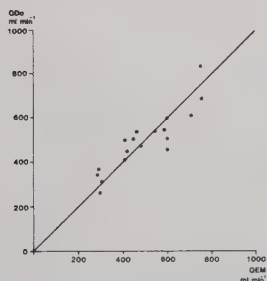


Figure 2a

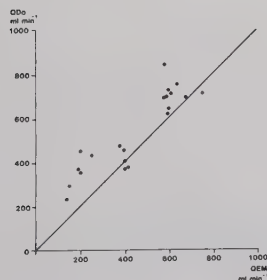


Figure 2b

Figure 2a, 2b, 2c. Correlation of the ultrasonically (QDo) and the electromagnetically (QEM) measured blood flow in animal No. 3, 4 and 5.

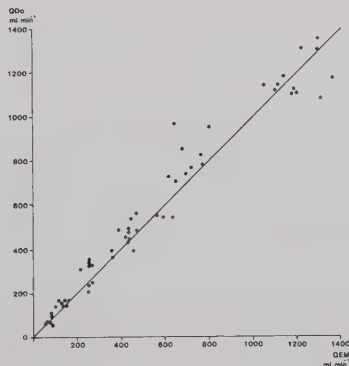


Figure 2c

Table I. Results of the simultaneous recording of the aortic blood flow in three pigs using Doppler ultrasound and electromagnetic flowmeter.

Animal number	Number of measurements	Mean difference QEM - QDo		$y = bx + a$	r^2	r	p-value
		Mean (%)	SD (%)				
3	18	-8.5	17.5	$y = 1.04x + 8.96$	0.83	0.91	<0.001
4	21	-11.2	14.8	$y = 1.16x + 171.6$	0.79	0.89	<0.001
5	57	-13.5	18.8	$y = 1.02x + 47.3$	0.96	0.98	<0.001

QEM = electromagnetically measured blood flow.

QDo = blood flow measured with the Doppler ultrasound method.

between 86 and 174 $\text{beats} \cdot \text{min}^{-1}$. The highest mean arterial blood pressure was 169 mm Hg and the lowest was 99 mm Hg. The mean blood velocity in the aorta varied between 5 and 92 $\text{cm} \cdot \text{s}^{-1}$. The mean aortic diameter was between 3.7 and 8.7 mm.

The correlation between blood flow measurements from the two methods is shown in Fig 2a, b, and c and in Table I. As seen in Fig. 3, the blood flow curves obtained by the electromagnetic flowmeter resembled those of the ultrasonically measured blood velocity during various hemodynamic conditions.

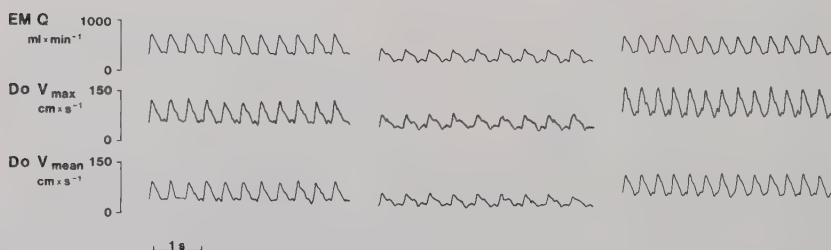


Figure 3. Examples of simultaneous recordings of the electromagnetically measured blood flow (EMQ) and the ultrasonically measured maximum (Do Vmax) and mean (Do Vmean) blood velocity. Recordings from the descending aorta of a pig were performed at various blood flow levels and heart rates.

On average the blood flow was overestimated 12.1% by the Doppler method compared to the electromagnetic method. The standard deviation of the difference between the two methods was 17.1%. There was no correlation between the difference in results of blood flow obtained from the two methods, and the heart rate, mean velocity or mean aortic diameter (Fig. 4).

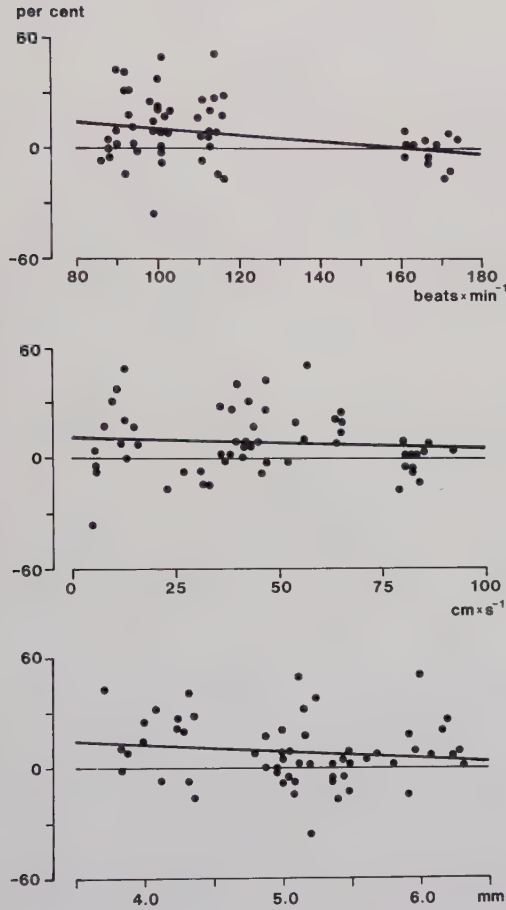


Figure 4. Relation between the percentual difference in the electromagnetically and ultrasonically measured blood flow (ordinate) and heart rate (upper part), mean blood velocity (middle part) and aorta diameter (lower part).

DISCUSSION

In the present experimental set-up the simulation of the fetal situation in utero was attempted. When blood flow is measured in the aorta or the intraabdominal part of the umbilical vein in the human fetus which is surrounded by amniotic fluid, the vessels are located approximately 8-12 cm away from the transducer. The fetal heart rate ranges from 110-180 beats $\cdot$ min $^{-1}$ and the aortic size ranges from 4-8 mm in the last weeks of pregnancy (9). The young domestic pigs used in the experimental study had comparable heart rate and aorta dimensions. The Doppler measurement was performed at a distance of 8-10 cm from the vessel. Ideally, the abdomen of the animal should have been closed to get tissue between the transducer and the vessel. This was not done as a preliminary experiment in which the abdomen was closed surgically gave us problems with air bubbles between the saline solution and the inner wall of the abdomen. It was also noticed in the preliminary studies that during apparently stable conditions as recorded by the Doppler method, the blood flow registered by the electromagnetic transducer showed great variations. These variations could be eliminated by a slight repositioning of the electromagnetic transducer. Additionally, the electromagnetic transducer had to be changed according to various vessel diameters.

Generally, there was a close resemblance between the results obtained by the two techniques evaluated. The correlation was linear over the examined flow range (Fig. 2a, b, c) and the difference between the results by the two methods did not seem to be influenced by the mean blood velocity, heart rate and vessel diameter (Fig. 4). On average, the Doppler method overestimated the blood flow when compared to the electromagnetic method. This can be partly explained by the highpass filter in the Doppler instrument. This filter was set at 100 Hz which is used for fetal blood flow examinations to eliminate high amplitude signals from the vessel walls or moving structures in the path of the beam. The lower portion of the Doppler frequency spectrum is then removed and the velocity estimators which calculate mean blood velocity above the filter cut-off, will show a slight

overestimation. For flow with a parabolic velocity profile, the offset corresponds to half the cut-off frequency of the filter (10). In our setup the insonation angle was 45° which corresponded to $2.7 \text{ cm} \cdot \text{s}^{-1}$ offset assuming parabolic flow. In vessels with pulsative flow, the velocity profile changes from nearly flat in the early systole to nearly parabolic in the late diastole. Thus, the influence of the high-pass filter on the calculated blood flow changes over the cardiac cycle and it cannot be measured exactly. Therefore, no correction for the high-pass filter was attempted in the calculations of blood flow in the present study. For the low velocity flow, the influence of the highpass filter is more pronounced (11). In our study, this was confirmed in the experiment on animal No. 5 (Fig. 2c), where the lowest flow values were measured and the largest overestimation of the Doppler method was found. For vessels ranging 4-6 mm, errors in the diameter measurement between 0.2 and 0.4 mm will cause errors in the flow measurement in the order to 10% (3). Thus, the systematic difference between the two methods is negligible when a correction is made for the influence of the highpass filter. The angle of insonation is also a source of error when working with the Doppler technique. In the present setup, however, the angle was kept under full control.

The electromagnetic method, generally accepted for invasive measurement of blood flow, was chosen in the present study as the method of reference. However, certain sources of error concerning the electromagnetic measurements became apparent during the study. The probe application on the vessel is a very important part of the reliability of the measurements. It has to be applied at a right angle to the vessel and it should fit the vessel properly and not obstruct the vessel lumen (12). The calibration of zero flow is a difficult and sensitive part of using the electromagnetic flowmeter and can cause systematic errors in the measurements (12,13,14). In this study, precautions were taken to avoid such errors as far as possible; calibration of the electromagnetic probes was done both in vitro and in situ, zero level was repeatedly estimated and proper positioning of the transducer on the vessel ensured. With the Doppler flowmeters

there are no problems affecting the zero calibration, since zero flow does not produce any Doppler-shifts.

Several studies have been published comparing the Doppler ultrasound blood flow measurements with other methods. Vattner et al. (15) made a simultaneous recording of blood flow on chronically prepared dogs and achieved errors of the Doppler measurements in the range of $\pm 5\%$. Alversson et al. (16) performed a similar comparison on femoral flow of newborn lambs and found a close agreement ($r=0.98$). Busija et al. (17) made measurements of cerebral blood flow in anesthetized rats and dogs and compared the Doppler techniques with the microsphere technique. They found correlation coefficients between the two techniques in the range of 0.94-0.98. Segadal et al. (18) did in vitro experiments and found a correlation coefficient of 0.91 between Doppler and electromagnetic techniques. They also described the problems associated with the calibration of electromagnetic transducers. The results of our experiment were consistent with the above studies.

Conclusively, the present study demonstrates that the combined pulsed Doppler technique (3) used under experimental conditions in an in vivo-like setup provides results which consistently are in agreement with the electromagnetic flowmeter. Thus, the ultrasound Doppler technique can be used to quantitate blood flow in fetal vessels if careful attention is paid to the various sources of errors (19). It is desirable that further studies on true in vivo setups be performed to assess the validity of the results since the method is becoming of increased importance for detailed noninvasive studies of the hemodynamic situation of the fetus in utero.

ACKNOWLEDGMENT

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ULTRASONIC MEASUREMENTS OF THE BLOOD VELOCITY AND PULSATILE DIAMETER
CHANGES IN THE FETAL DESCENDING AORTA

Göran Lingman, M.D., Gerhard Gennser, Ph.D., and Karel Maršál, Ph.D.

Department of Obstetrics and Gynaecology, University Hospital, Malmö,
Sweden

ABSTRACT

External fetal ECG was used in the synchronization of subsequent measurements of the fetal aortic blood velocity by the pulsed Doppler technique and of the vessel diameter by real-time ultrasound with an echo-tracker. The pulsatile changes of the two parameters were measured in the thoracic descending aorta of 10 term fetuses. The onset of the increase in the aortic diameter and in the blood velocity was almost simultaneous; the peak velocity occurred 37 msec before the peak diameter. The aortic stroke volume was 5.4 ml (1.8 ml/kg). The "effective" diameter of the aorta calculated from the synchronized integrals of the diameter and blood velocity signals was 0.21 mm larger than the mean of the systolic and diastolic diameters. This difference in the diameter may have an impact on the calculation of the volume blood flow.

INTRODUCTION

Recently, the ultrasonic method combining the pulsed Doppler technique and B-mode imaging enabled a non-invasive assessment of the blood flow in the umbilical vein (6) and in the fetal descending aorta (2). The volume blood flow is calculated from the mean blood velocity and from the mean diameter of the vessel. The blood velocity and the vessel diameter, however, cannot be measured simultaneously due to the interference of the two ultrasound techniques. In arteries, the pulsatile changes of the vessel diameter and of the blood velocity are not simultaneous (8); this is not taken notice of when measurements of the two parameters are performed subsequently. However, it is unknown to what degree this fact influences the calculated blood flow. This paper describes an attempt to circumvent the problem of the ultrasound interference and to elucidate the relationship between the vessel diameter and the blood velocity in the human fetal aorta.

METHODS AND MATERIAL

The ultrasound measurements of the fetal aortic blood velocity and of the pulsatile changes of the vessel diameter were synchronized using abdominal fetal ECG. In the same fetus, subsequent measurements of the vessel diameter and of the blood velocity were performed on the thoracic descending aorta.

Fetal ECG was obtained from three electrodes placed on the maternal abdomen at the midline. An electrocardiograph with a subtraction system (11) including an ultra-sensitive isolation amplifier was utilized.

The aortic blood velocity was measured by the combined pulsed Doppler and real-time ultrasound technique (2). A real-time linear array ultrasound scanner (ADR, Tempe, Arizona, 3.5 MHz) was used for the localization of the vessel. The real-time transducer was placed parallelly to the fetal aorta which was then insonated by the 2 MHz pulsed Doppler instrument (ALFRED, Vingmed, Norway). The Doppler transducer was attached to the real-time transducer at a fixed angle

of 45° . This technique enabled a correction of the measured blood velocity for the angle between the ultrasound beam and the blood flow direction. Doppler shift signals were analysed with a spectrum analyser (DAISY, Vingmed, Norway) and the mean and maximum blood velocities were automatically estimated on-line (7). The analogue signals of the blood velocities were recorded on a polygraph simultaneously with the fetal ECG signals.

The pulsatile changes of the aortic diameter were recorded by a pulsed ultrasound echo tracker using a phase-locked loop system (Teltec, Lund, Sweden) built into the real-time linear array scanner. The spatial resolution of the system was $30 \mu\text{m}$ at 1.28 kHz repetition frequency (4). The aorta diameter signals were recorded simultaneously with the fetal ECG signals.

The fetal QRS complexes were used for the calculation of the fetal heart rate (FHR), the selection of the equal beat-to-beat intervals (maximum allowed difference 5%) and for the synchronization of the blood velocity and the aorta diameter curves.

The synchronized diameter and mean blood velocity signals were analysed with a microcomputer including a digitizer. The blood velocity signals were corrected for the delay of 20 msec caused by the mean velocity estimator. The time relations between the velocity and diameter curves were studied. The aortic stroke volume was calculated by the formula

$$Q = \frac{t \int V \cdot d^2 \cdot \pi}{4 \cdot \cos 45^{\circ}}$$

(Q = aortic stroke volume; V = blood velocity; d = diameter of the aorta). The calculations were performed for 8 cardiac cycles in each fetus by integrating 50 synchronized sections per cycle of the diameter and of the blood velocity traces. The aortic stroke volume (Q) was also related to the fetal weight estimated from the ultrasonically measured fetal head and abdominal diameters (1).

From the values of the volume blood flow (Q') in ml/min ($Q' = Q \cdot \text{FHR}$) based on the synchronized calculations and from the values of the

time-average mean velocity (V), an "effective" diameter (D_{eff}) was obtained according to the formula

$$D_{\text{eff}} = \sqrt{\frac{4 \cdot Q}{V \cdot \pi \cdot 60}}$$

The "effective" diameter was then compared with the systolic and diastolic diameters measured with the echo tracker.

Student's t-test for paired observations was used for statistical evaluations.

The measurements were performed on the descending aorta of 10 normal term fetuses. The level of the measurement was just above the fetal diaphragm. The gestational age of the fetuses was between 36 and 40 weeks as ascertained by the ultrasound fetometry in early pregnancy.

RESULTS

The mean FHR based on the beat-to-beat intervals of the measured cardiac cycles was 135.5 ($SD \pm 4.9$) beats/min. The time-averaged mean velocity was 33.0 (± 4.4) cm/s. The average systolic and diastolic diameters were 7.3 (± 1.1) and 6.3 (± 1.1) mm, respectively.

The time relation between the synchronized aortic diameter and the blood velocity traces is schematically presented in Fig. 1.

The onset of the diameter change preceded the onset of the velocity increase on average by 7 (± 9) msec (n.s.). The systolic diameter occurred 37 (± 13) msec after the velocity had reached its peak ($p < 0.01$).

The mean aortic stroke volume (Q) was 5.4 (± 1.6) ml and the relative aortic stroke volume was 1.8 (± 0.5) ml/kg.

The average "effective" aortic diameter (D_{eff}) was 7.0 (± 1.1) mm which was significantly higher (mean difference 0.21 (± 0.07) mm ($p < 0.01$)) than the mean aortic diameter calculated from the diastolic and systolic diameter values (Fig. 2).

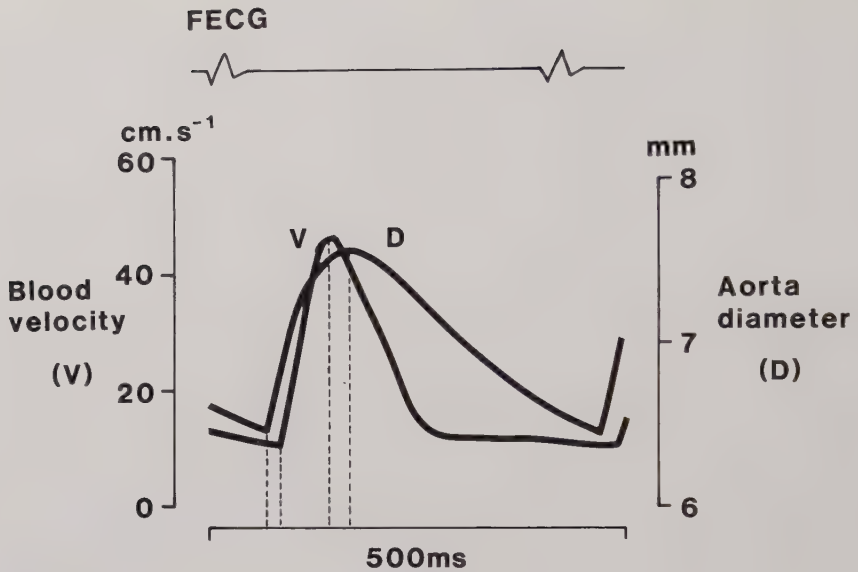


Figure 1. Course of the mean blood velocity (V) and the vessel diameter (D) during one cardiac cycle in the thoracic descending aorta of the human fetus. The schematic picture is based on the measurements in 10 term fetuses. The subsequent measurements of the two parameters were synchronized by the external fetal electrocardiogram (FECG).

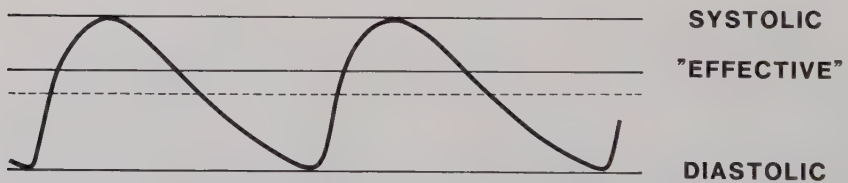


Figure 2. Schematic diagram of the pulsatile changes of the aortic diameter in term fetus. The "effective" diameter of the aorta was calculated from the blood flow values based on the synchronized measurements of the blood velocity and the diameter and from the mean blood velocity values. The "effective" aortic diameter was significantly larger than the mean diameter (broken line) calculated as the average of the systolic and diastolic diameters.

DISCUSSION

The recently developed ultrasonic method for the measurement of the human fetal blood flow (2, 6) is an important contribution to our possibilities of evaluating the fetal circulation in utero. However, when using the combined pulsed Doppler and real-time method for fetal blood flow measurements, it is necessary to be aware of its limitations and pitfalls (3). One of the main drawbacks of the method is the impossibility to simultaneously measure the blood velocity and the vessel diameter because of the ultrasound interference. This is especially disadvantageous when measuring pulsatile arterial flow. At the present time, the technical difficulties of the simultaneous use of the two techniques have not been overcome. This paper gives an indirect solution to the problem by subsequent ECG-synchronized recordings of the fetal blood velocity and the vessel diameter. A similar method was used by Tonge et al (10) for the calculation of the aortic stroke volume. In our study, also the time relation between the diameter changes and velocity curves was analysed (Fig. 1).

The mean time lag between the onsets of the two curves (7 msec) was close to the time resolution limit of the digitizer used for the computerized curve analysis. Thus, the onsets of the vessel expansion and the flow velocity were probably almost simultaneous or at least with a minimum time lag. However, the peak blood velocity occurred before the peak diameter, the time lag being significant. A similar relationship was described for the blood flow and the blood pressure courses in the abdominal aorta (9) and femoral artery (8) in animal experiments.

The calculation of the fetal volume blood flow from the ultrasonically gained data on the blood velocity and the diameter of the vessel is open to many errors (3, 5). The main source of error seems to be the measurement of the vessel diameter (2). The use of a Time-Distance recorder for the dynamic measurement of the fetal aortic diameter (2) respects the pulsatile character of the aortic flow and decreases the possibility of error. However, the time lag between the velocity and the diameter courses occurring within one cardiac cycle

has not been previously considered. Our present results show that the difference between the "effective" and the mean aortic diameter measured above the level of the fetal diaphragm was 0.21 mm. This difference causes an error in the resulting volume blood flow of 6%. Before any conclusion can be reached, of whether or not to correct the volume blood flow results for the time lag between the two curves, it is necessary to confirm our preliminary results on larger material at various gestational ages and in measurements at different sites on the fetal aorta.

The aortic stroke volume calculated by us was slightly higher than that given by Tonge et al (10). The gestational age of the fetuses and their aortic diameters were similar in the two studies. Thus, the difference in the aortic stroke volume was probably due to the differences in the mean blood velocity. A possible explanation to this might be the use of different high-pass filters for filtering the Doppler shift signals (100 Hz in the present study versus 150 Hz in the study (10).

The synchronization of the ultrasound recordings of the fetal aortic blood velocity and the fetal aortic diameter by the external fetal ECG proved to be a suitable method for increasing the accuracy of the fetal blood flow measurements. However, the method is laborious and can hardly be used in a clinical situation. Nevertheless, it can be recommended for physiological and experimental studies on human fetal circulation.

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FETAL CENTRAL BLOOD CIRCULATION IN THE THIRD TRIMESTER OF NORMAL
PREGNANCY - A LONGITUDINAL STUDY

I. Aortic and Umbilical Blood Flow

Göran Lingman and Karel Maršál

From the Department of Obstetrics and Gynecology, General Hospital,
University of Lund, Malmö, Sweden

SUMMARY

Fetal central blood circulation was evaluated in 21 uncomplicated pregnancies every other week from the 27th gestational week till term. Blood flow in the fetal descending thoracic and abdominal aorta and in the intra-abdominal umbilical vein was measured with a combined ultrasound real-time and 2 MHz pulsed Doppler technique. The mean fetal blood velocities were fairly constant at the three measuring sites during the last trimester: $34.6 \text{ cm} \cdot \text{s}^{-1}$ (SD 5.5), $32.7 \text{ cm} \cdot \text{s}^{-1}$ (SD 5.5) and $12.6 \text{ cm} \cdot \text{s}^{-1}$ (SD 3.1), respectively. The aortic diameter increased with gestational age, whereas the umbilical vein diameter increased until the 34th gestational week followed by a stagnation. The mean weight related blood flow in the fetal thoracic descending aorta decreased slightly towards term (from $240.8 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (SD 53.6) in the 28th week to $212.6 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (SD 37.3)). In the umbilical vein, the corresponding blood flow decrease was linear and more pronounced: from $138.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (SD 76.0) to $65.2 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ (SD 14.2). The results indicate that the placental proportion of fetal blood flow decreases with gestational age.

Key words: Fetal blood circulation - normal pregnancy - fetal aortic blood flow - umbilical blood flow - ultrasound

INTRODUCTION

Before ultrasound technology became available for obstetric use, direct measurement of the human fetal circulation was impracticable. Fetal heart rate recording by means of continuous wave Doppler ultrasound was introduced in 1966 (1). Fitzgerald & Drumm (10) used continuous wave Doppler ultrasound for waveform analysis of blood velocity in the umbilical arteries. Pulsed Doppler technique enabling depth resolution, was presented by McCallum (22) for the same purpose. The first ultrasonic estimation of the human umbilical blood flow was published in 1979 (11). Eik-Nes et al. (5) used combined pulsed Doppler and real-time linear array ultrasound technique to measure blood flow in the fetal descending aorta; this technique was subsequently used by several groups in clinical and pharmacological studies (13,16,18,23,26). Recently, a study was published on serial examinations of fetal aortic blood flow measured by means of a duplex system combining pulsed Doppler and a mechanical sector scanner (9).

The Doppler ultrasound method for the measurement of fetal blood flow is being increasingly applied in clinical obstetrics. For the proper interpretation of clinical results it is necessary to collect background data on the physiology of human fetal circulation. The purpose of the present study was to examine the development of circulation in central fetal vessels during the third trimester of pregnancy. This paper (part I) presents the results of volume blood flow measurements, whereas part II (19) describes the aortic blood velocity waveform.

MATERIAL AND METHODS

Thirty-one women with ultrasonically dated pregnancies entered the study and were examined on alternate weeks from the 27th gestational week till term. Subsequently, ten women had to be excluded due to pregnancy complications (pre-eclampsia, premature labor, placenta abruption). The remaining 21 healthy pregnant women constituted the

study group. In the following, only results from those 21 normal pregnancies are presented.

The median age of the 21 women was 29 years (range 22 to 36 years). Eight women were nulliparae, 10 primiparae and 3 multiparae. Five women were smokers; none of the women received any medication during the pregnancy other than iron supplementation.

Nineteen women gave birth spontaneously per vaginam; 2 were delivered by means of cesarean section (1 fetopelvic disproportion; 1 imminent fetal asphyxia during labor). The median gestational age at delivery was 39 weeks 6 days (range 36 weeks 3 days to 42 weeks 3 days). Fourteen neonates were males and 7 females. The median birth weight was 3,560 g (range 2,530 to 4,580 g); all weights were appropriate for gestational age. The birth weight of the infant born before 37 completed gestational weeks was 3,170 g. All newborns had an Apgar score ≥ 8 at 1 minute and ≥ 9 at 5 minutes post partum.

A combination of a 2 MHz pulsed Doppler instrument (ALFRED, Vingmed A/S, Oslo, Norway) and a real-time linear array scanner (ADR, Model 2130, Advanced Diagnostic Research Corporation, Tempe, Arizona) was used for the fetal blood flow measurements. The output ultrasound energy of the pulsed Doppler instrument was reduced and measured; following ultrasound intensities were found at the surface of the transducer: SATA $27 \text{ mW} \cdot \text{cm}^{-2}$, SPTA $103 \text{ mW} \cdot \text{cm}^{-2}$, SPTP and SPPA in the order of 1000 and $800 \text{ mW} \cdot \text{cm}^{-2}$, respectively (for definitions see ref. 25). The real-time scanner produces output ultrasound energy of $0.2 \text{ mW} \cdot \text{cm}^{-2}$ (SATA) according to the manufacturer.

The instrumental set-up is described in detail elsewhere (8). The pulsed Doppler transducer was attached to the real-time transducer at a fixed angle of 45° thus enabling correction of the measured blood velocity for the angle. The recorded Doppler shift spectrum was analysed by means of Fast Fourier Transform (DAISY, Vingmed A/S, Oslo, Norway) and the maximum and the mean velocities were automatically estimated on-line. A 100 Hz high-pass filter was used to eliminate Doppler shift frequencies caused by vessel wall movements. The diameter of the vessel was measured in 10 subsequently frozen real-time images of the vessel in longitudinal section. Measuring was done

from the outer to the inner outline of the vessel wall echo, using electronic calipers operating in 0.4 mm steps. The cross-sectional vessel area was calculated from the mean diameter assuming the vessel to be circular. Volume blood flow was then calculated according to the formula:

$$Q = \frac{V \cdot A}{\cos 45^{\circ}}$$

(Q = volume blood flow, V = time-averaged mean blood velocity, A = cross-sectional vessel area). The volume blood flow was related to the fetal weight estimated from the ultrasonically measured biparietal diameter and mean abdominal diameter (7).

Fetal blood flow was measured in the middle part of the thoracic descending aorta, in the abdominal descending aorta 1-2 cm above the bifurcation, and in the intraabdominal part of the umbilical vein. Only recordings obtained during fetal apnea and motor inactivity were accepted. Measurements of the blood velocities were always performed both upstream and downstream to examine the reproducibility of the velocity measurements and to evaluate whether or not there was any systematic angle error. Altogether 136 blood flow measurements were performed - on average 6.5 per pregnant woman. On all recording occasions the fetuses were in longitudinal position; on 23 occasions the fetus was in breech presentation. The success rate for the three measuring sites related to the presentation of the fetus and direction of the insonation (upstream vs. downstream) is presented in Table I.

The use of a high-pass filter caused a systematic overestimation of the mean blood velocity in the umbilical vein with a parabolic flow profile (8). Correction was therefore made for the offset by subtracting $2.71 \text{ cm} \cdot \text{s}^{-1}$ (half of the cut-off frequency level for 100 Hz filter at 45° insonation angle) from the recorded umbilical mean blood velocity. The aortic stroke volume was calculated by dividing the blood flow by fetal heart frequency. The proportional blood flow to viscera, lower extremities and placenta was calculated from the values obtained at the three measuring sites. Correlation was examined between the umbilical blood flow obtained at the last recording in each fetus and the placenta weight and birth weight, respectively.

All women participated in the study after giving their informed consent. Smokers among the women were asked to abstain from smoking for at least 1 hour before the examination, which took place between 10 and 12 a.m. and lasted on average for 40 min after a setting-in period of 10 min. All measurements were made by one of the authors (G. L.) to eliminate the interobserver variation. During recording the women rested in a semirecumbent position, tilted 15° to the left to avoid the vena cava syndrome.

The statistical analysis of the results was performed with the BMDP (Biomedical Computer Programs, UCLA, Dept. of Biomathematics, California); t-test for paired observations and linear correlation were used.

Table I. Success rate of fetal blood flow measurements at the three recording sites in relation to fetal presentation and direction of insonation.

	Thoracic aorta (%)	Abdominal aorta (%)	Umbilical vein (%)
Cephalic presentation			
measurement upstream	100	88	-
measurement downstream	83	90	-
Breech presentation			
measurement upstream	83	83	-
measurement downstream	78	61	-
All presentations			
measurement upstream	96	84	87
measurement downstream	83	89	80
all measurements	98	91	90

RESULTS

There were no statistical differences between blood velocities recorded upstream and downstream at either of the measuring sites (Fig. 1).

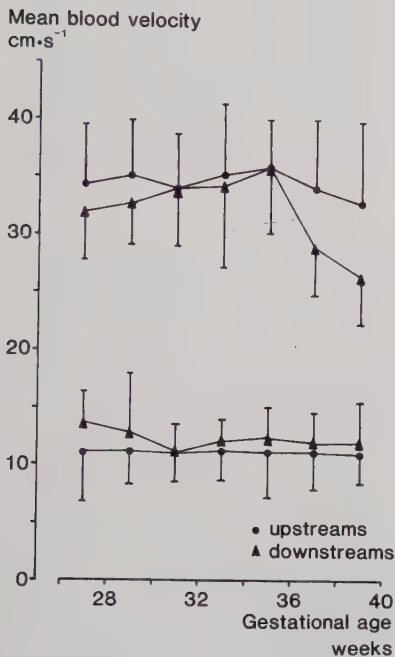


Figure 1. Mean blood velocities in the thoracic descending aorta (upper part) and umbilical vein (lower part) in relation to gestational age and direction of measurement (Mean $\pm$ SD; n = 21).

Thoracic descending aorta

A typical recording of the pulsatile blood velocity indicating forward flow throughout the whole cycle is presented in Fig. 2. During systole, all Doppler shift frequencies are closely collected and low velocities are lacking. During diastole, a subsequent spread of the frequencies is demonstrated. The time-averaged mean blood velocity did not alter significantly with gestational age (Fig. 3); the mean

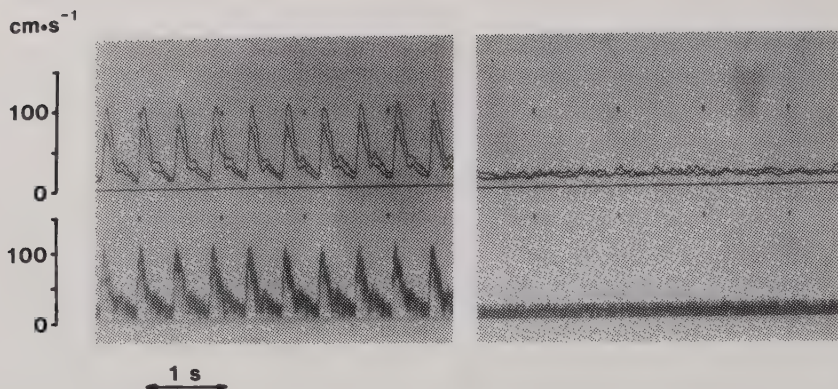


Figure 2. Blood velocity signals recorded from the descending thoracic aorta (left) and umbilical vein (right) of a 34-week-old fetus. Analogue signals of the maximum and mean velocities (upper part) were estimated on-line from the Doppler shift spectrum (lower part). Calibration was corrected for the insonation angle of 45° .

value for the period of gestation studied was $34.6 \text{ cm} \cdot \text{s}^{-1}$ (SD 5.5). The aortic diameter increased linearly with gestational age (Fig. 3) and was correlated to the fetal weight ($r = 0.87$).

The linear increase in the blood flow until 36 weeks of gestation was followed by a flattening till term (Fig. 3). The correlation coefficient (r) between the blood flow uncorrected for fetal weight and the gestational age was 0.72. The stroke volume changed with gestational age in a pattern similar to that for blood flow (Fig. 3).

The vessel area per kg fetal weight was constant throughout pregnancy (mean $0.136 \text{ cm}^2 \cdot \text{kg}^{-1}$; SD 0.025) (Fig. 4). The relative blood flow ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) was stable till 36 gestational weeks, whereafter a fall was noted (Fig. 4; Table II). The mean weight-related aortic stroke volume was $1.74 \text{ ml} \cdot \text{kg}^{-1}$ (SD 0.32).

Abdominal aorta

The mean blood velocity was constant during the observation period

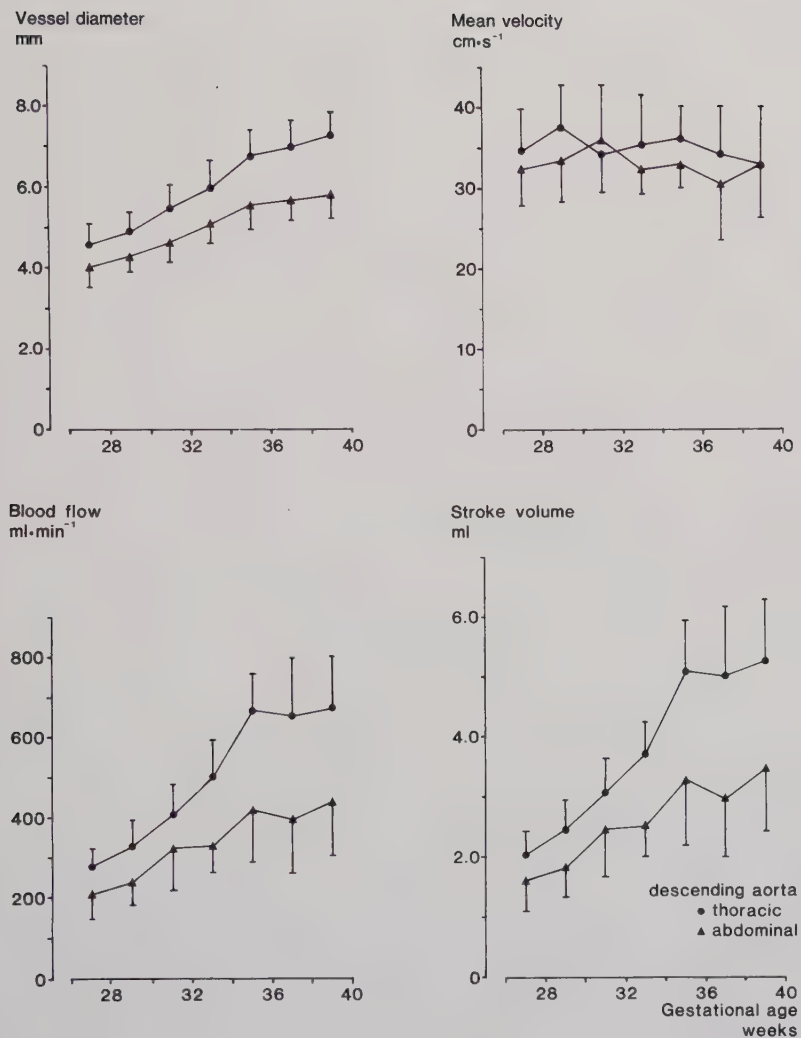


Figure 3. Changes with gestational age in diameter, blood velocity, blood flow, and stroke volume, measured in the descending thoracic and abdominal aorta of normal fetuses (Mean $\pm$ SD; n = 21).

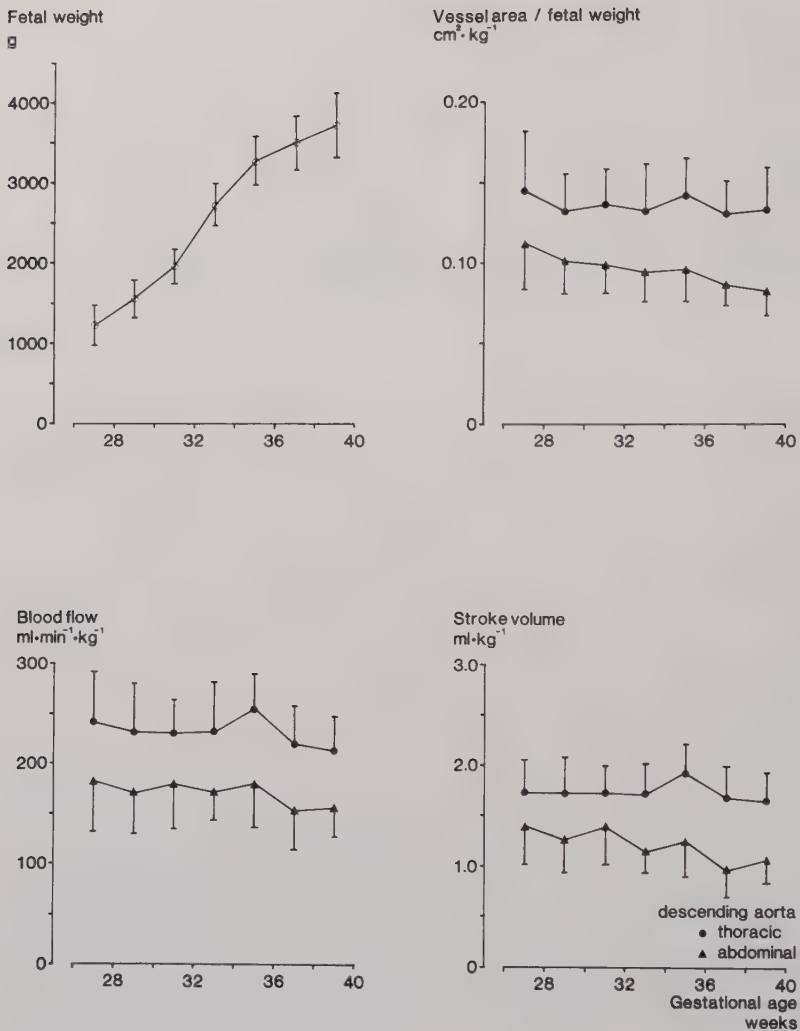


Figure 4. Changes with gestational age of the ultrasonically estimated fetal weight and weight-related cross-sectional vessel area, blood flow and stroke volume measured in the descending thoracic and abdominal aorta of normal fetuses (Mean $\pm$ SD; n = 21).

and did not differ significantly from the mean velocity recorded in the thoracic aorta (Fig. 3). The mean value for the last trimester was $32.7 \text{ cm} \cdot \text{s}^{-1}$ (SD 5.5). A linear relation was found between the diameter and the gestational age ($r = 0.75$) (Fig. 3). Both blood flow and stroke volume increased with gestational age (Fig. 3), the correlation coefficients being 0.52 and 0.51, respectively. Vessel cross-sectional area, volume blood flow and stroke volume related to fetal weight decreased slightly as gestation progressed (Fig. 4; Table II), the correlation coefficients being -0.32, -0.35 and -0.31, respectively.

Table II. Fetal blood flow values, for three periods of the last trimester of pregnancy ($\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$) (mean $\pm$ SD).

	Gestational weeks		
	27 - 36	37 - 38	39 - 40
Descending thoracic aorta	237.9 (45.6)	221.0 (41.4)	212.6 (37.3)
Abdominal aorta	168.9 (43.2)	133.2 (38.2)	135.8 (30.4)
Umbilical vein	114.8 (42.6)	76.3 (24.6)	65.2 (14.2)

Umbilical vein

The blood flow was steady and continuous (Fig. 2). The time-averaged mean blood velocity did not change with gestational age (Fig. 5); the mean value for the study group was $12.6 \text{ cm} \cdot \text{s}^{-1}$ (SD 3.1). The vessel diameter showed an increase with gestational age till 36 weeks whereafter it reached a plateau (Fig. 5). The coefficient of correlation between vessel diameter and gestational age was 0.52. The weight-

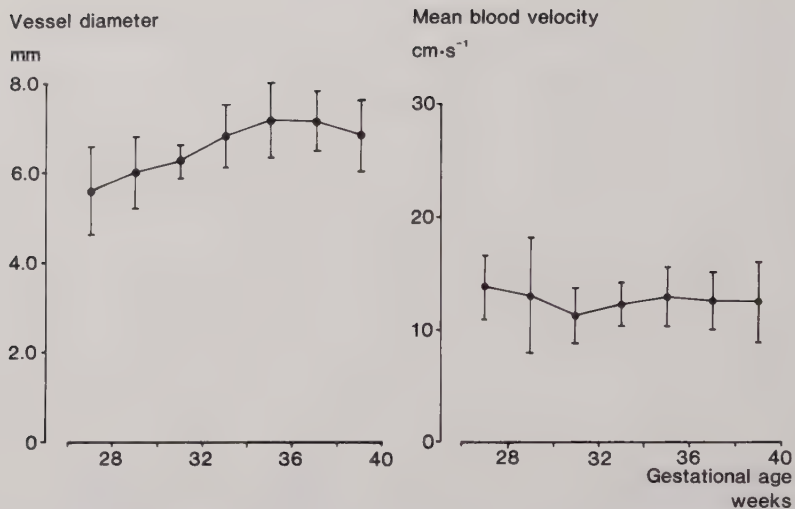


Figure 5. Development with gestational age of the diameter and mean blood velocity measured in the intra-abdominal part of the umbilical vein of normal fetuses (Mean $\pm$ SD; n = 21).

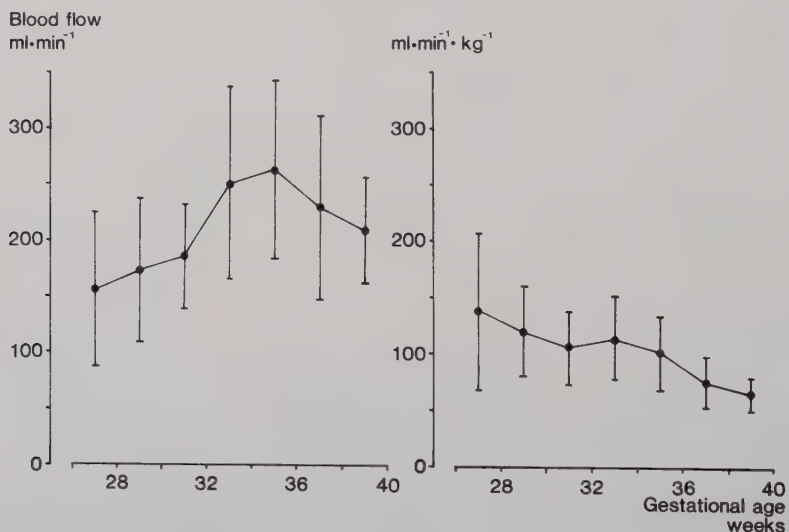


Figure 6. Umbilical venous blood flow in relation to gestational age in 21 normal fetuses (mean $\pm$ SD).

related cross-sectional area of the vessel decreased as gestation progressed ($r = -0.62$). Changes in the blood flow with gestational age are demonstrated in Fig. 6 and Table II. Blood flow related to fetal weight decreased linearly towards term ($r = -0.50$).

Distribution of blood flow

Fig. 7 presents schematically the percentage distribution of the blood flow in the fetal thoracic descending aorta which is given as 100%. The placental proportion of the blood flow decreased subsequently from 59% in the 28th gestational week to 33% at term, whereas the flow to viscera and to lower extremities increased from 22% to 39% and from 19% to 28%, respectively.

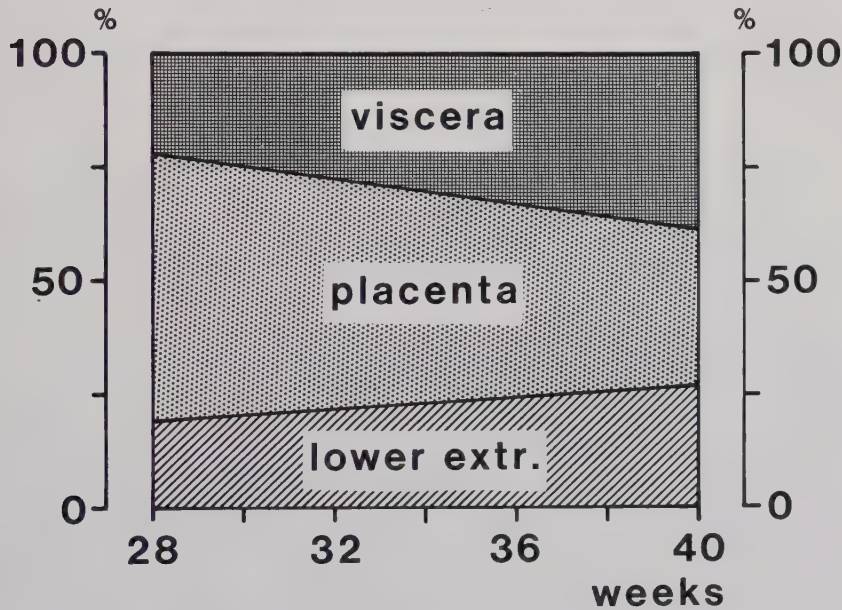


Figure 7. Distribution of the fetal aortic blood flow and its development during the third trimester of normal gestation. Blood flow in the thoracic part of the fetal descending aorta is given as 100%.

Correlation between the last umbilical blood flow and the placenta weight was stronger than between the umbilical flow and the birth weight, correlation coefficients (r) being 0.83 and 0.45, respectively. The mean umbilical flow related to the placenta weight was $50.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ (SD 6.7).

The relationships between the vessel diameters at the three sites of measurement were evaluated by forming ratios: the three ratios increased linearly with gestational age (Fig. 8). The mean ratio between the thoracic aorta and umbilical vein exceeded 1.0 only in the last 2-week examination period.

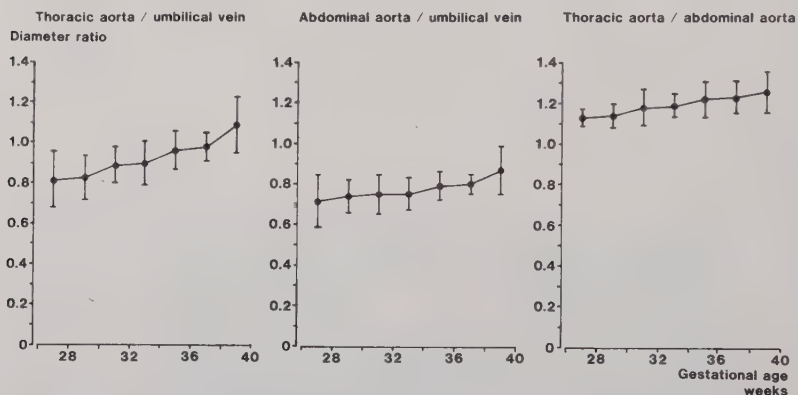


Figure 8. Vessel diameter ratios calculated from the three measuring sites and related to the gestational age (Mean $\pm$ SD).

DISCUSSION

Human fetal blood flow was measured in normal pregnancies using a combined ultrasound method. The accuracy of the ultrasound method has been previously tested against the electromagnetic flowmeters in animal experiments and highly significant correlations have been found (8). Such close correlations and reliable results, however, can be obtained only when the possible errors of the method are taken into account. In the present study, the utmost care was taken to minimize the influence of such errors.

Our previous methodological studies demonstrated that the maximum error in the measurement of the vessel diameter was 0.4 mm (6), and the maximum error in the insonation angle 5° (8). The latter was supported by the fact that in the present study no significant differences were revealed between the results obtained when measuring the flow velocities upstream and downstream, respectively (Fig. 1). To minimize errors due to the filtering of the Doppler shift signals the lowest possible cut-off level (100 Hz) of the filter was used. Furthermore, the mean velocity recorded from the vessel with a parabolic flow profile (i.e. the umbilical vein), correction for the off-set was consequently performed. The used ultrasonic method of estimating fetal weight was found to have a maximum error of 20% (7); in the present study group, the fetal weight was overestimated by a mean of 3.2% (SD 8.5%) (unpublished data). No correction for the nonsimultaneous pulsatile changes in the blood velocity and the vessel diameter of the fetal aorta was attempted. This because the effects of this factor have been so far evaluated only for a relatively narrow range of the gestational age and fetal heart rate (17).

The sum of the above described errors can in extreme cases be considerable and give rise to the wide variation in the blood flow results (Fig. 4). However, at present, it is impossible to distinguish between the influence of the methodological factors and the physiological variation which was demonstrated to be appreciable - at least in fetal lambs (3).

The immediate reproducibility of the blood velocity measurements at the three sites was tested in the present study by comparing velocities measured both upstream and downstream. There was no significant difference in the results obtained by the two modes of measuring. However, due to the shape of the maternal abdomen, the easiest way to measure the aortic blood flow in fetuses in cephalic presentation was upstream in the thoracic aorta and downstream in the abdominal aorta (Table I).

No adverse effects on the human fetus have been until now demonstrated for the diagnostic ultrasound. Nevertheless, we considered it important to reduce the ultrasound output energy of the pulsed Doppler

instrument when using it on pregnant women. After the reduction, the measured output energy levels were within the recommended safety limits and below the intensity ranges of the commercially available pulsed Doppler instruments (2). The high quality of the Doppler signals was still retained.

The blood flow values found in the thoracic descending aorta exceed those obtained in a previous study (6). This is probably due to better defined and uniform sites of measurement in the present study where the intrathoracic measurements were performed between the distal part of the aortic arch and the diaphragm and in the abdominal aorta just proximal to the aortic bifurcation. Another important difference between the two studies was the use of high-pass filters with different cut-off levels: in the present investigation 100 Hz filter was used, whereas Eik-Nes et al. (6) used 400 Hz filter which eliminated a considerable proportion of the diastolic flow signals. The results in the present study were consistent with cross-sectional studies published by us (21) and by others (13). Only one longitudinal study has so far been published on the aortic fetal blood flow (9). In that study the mean value of flow in the fetal abdominal aorta was somewhat higher than our results, probably attributable to the use of a different type of ultrasound equipment (duplex sector scanner) which has some disadvantages for fetal blood flow measurements - a small sample volume and difficulties in achieving a small insonation angle.

The blood velocities in the thoracic part of the descending aorta were found to be relatively constant during late pregnancy. The growth of the aorta diameter paralleled the changes in fetal weight with gestational age. This was also confirmed by the fact that the vessel cross-sectional area per unit weight ($\text{cm}^2 \cdot \text{kg}^{-1}$) did not change over time. The volume blood flow increased up to 36 weeks, whereafter a plateau was seen. This plateau was not as obvious when the volume blood flow was corrected for fetal weight, although a small decline of the weight-corrected blood flow could still be seen. This was also found by Griffin et al. (13).

Despite the decrease in the aortic blood flow, the aortic stroke volume did not diminish towards term. This was due to the decreasing

fetal heart rate near term (7.2%) which was in accord with previous reports (4). The finding of the mean aortic stroke volume of $1.74 \text{ ml} \cdot \text{kg}^{-1}$ was consistent with the previously reported stroke volume calculated from the recordings of the aortic mean velocity and diameter synchronized with fetal ECG (17).

The mean blood velocity recorded in the abdominal aorta was similar to that found in the thoracic aorta and comparable to values reported by Eldridge and Berman (9) ($31\text{-}34 \text{ cm} \cdot \text{s}^{-1}$). The diameter of the abdominal aorta increased with gestational age but the slope of the diameter growth curve was not as steep as for the thoracic aorta (Fig. 3). Consequently, the cross sectional area of the abdominal aorta per unit fetal weight decreased with time. The resulting slight decline in the relative volume flow is consistent with the concomitant decrease in the placental circulation (Fig. 7).

The diameter of the umbilical vein increased up to 34 gestational weeks, followed by a flattening of the diameter growth curve. The increase in the cross-sectional area was thus not proportional to the growth of the fetal body. Umbilical blood flow increased up to 36 gestational weeks, whereafter a decline in the flow was seen. The weight-related flow showed a continuous decline throughout the period of pregnancy studied. This decrease in flow in the umbilical vein was also found by others in cross-sectional ultrasonic studies on the human fetus (12,15) and in experimental studies on animals (3).

Our study demonstrated that fetal blood velocity did not change significantly as gestational age progressed and that the increase in flow was mainly due to the growth of the diameter of the vessels studied. This growth was, however, not proportional to the growth of the fetal body and it differed at various sites of measurement. The relationship between the diameters of various vessels was characterized by ratios (Fig. 8). Changes in the ratios of vessel diameters according to gestational age reflected the changing distribution of blood flow within the fetus.

To our knowledge, no reports describing the distribution of blood flow in the human fetus have hitherto been published. Longo et al. (20) found that 62% of the flow in the descending aorta of the sheep

fetus was led to the placenta. In our study, of the flow in the abdominal aorta, 76% in the 28th gestational week and 54% in the 40th week was distributed to the placenta (Fig. 7). Thus, the proportion of the placental flow diminished as gestation progressed while both the visceral flow and the flow to the lower extremities increased. This redistribution of the blood flow was also found in other species (24) and is probably due to the discordant growth of the placenta and the fetal body during the last weeks of pregnancy (14). Further support to this explanation was given by the fact that, in the present study, the umbilical blood flow correlated better with the placental weight than the birth weight.

This longitudinal study analysed blood flow and its distribution in the human fetus and described the changes occurring with gestational age. The variations in the results were rather large, as they comprised both the methodological errors, physiological intra-individual variations and inter-individual differences. More information on the fetal circulation can be obtained by analysing the waveform of the fetal arterial maximum velocity. It is an advantage that the parameters of the maximum blood velocity waveform are less sensitive to methodological errors. Results of the waveform analysis of the fetal aortic velocity recorded from the present material will be presented in part II.

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FETAL CENTRAL BLOOD CIRCULATION IN THE THIRD TRIMESTER OF NORMAL
PREGNANCY - A LONGITUDINAL STUDY

II. Aortic Blood Velocity Waveform

Göran Lingman and Karel Maršál

Department of Obstetrics and Gynecology, General Hospital, University
of Lund, Malmö, Sweden.

SUMMARY

Waveform of the maximum blood velocity recorded from the fetal descending thoracic and abdominal aorta was analyzed in a longitudinal study on 21 normal pregnancies from the 27th gestational week till term. Measurements of blood velocity were performed with combined real-time linear array and 2 MHz pulsed Doppler ultrasound technique every second week. The rising (RS) and the descending (DS) slopes did not change with gestational age in the thoracic descending aorta. The peak maximum velocity, the pulsatility index (PI) and the acceleration time percentage were constant during the last trimester of pregnancy, in both the thoracic and the abdominal aorta. In the former, the mean RS was 29.9 (SD 4.9), mean DS 5.3 (SD 0.9), mean peak velocity 115.6 $\text{cm}\cdot\text{s}^{-1}$ (SD 19.0), mean PI 1.96 (SD 0.31) and the mean acceleration time percentage 19.2% (SD 2.2). In the abdominal aorta, the mean RS was 25.7 (SD 5.6), mean DS 4.5 (SD 0.9), mean peak velocity 99.7 $\text{cm}\cdot\text{s}^{-1}$ (SD 18.8), mean PI 1.68 (SD 0.28) and the mean acceleration time percentage 19.1% (SD 2.2). The PI and the DS, considered to reflect mainly peripheral vascular resistance, were mutually related ($r=0.72$). The acceleration time percentage, RS and PI did not show any significant relation to fetal heart rate or gestational age which justifies the use of gestational age-independent reference values for those parameters during the last 3 months of gestation, at least within the normal fetal heart rate range.

INTRODUCTION

The first measurements of fetal placental blood velocity were performed by Haselhorst et al. (9) who used a dye dilution method. Stempera (17) estimated blood circulation velocity in the umbilical cord by means of a glucose dilution method and demonstrated an impaired circulation in imminent fetal asphyxia. Later, ultrasound technique for assessment of blood velocity in umbilical arteries was introduced - both continuous wave (5) and pulsed wave (15) Doppler ultrasound were used for this purpose. The use of pulsed Doppler technique made depth resolution possible (15).

It has been demonstrated that blood velocity waveform in the umbilical arteries changes with progress of pregnancy indicating a subsequent lowering of the peripheral resistance in the placental vascular bed (16). In growth-retarded fetuses, the waveform of the umbilical arterial blood velocity points to an increased peripheral vascular resistance (16). Also in the descending aorta of growth-retarded fetuses, typical waveform changes of the maximum blood velocity have been described (8,11,12). In these studies the combined real-time and pulsed Doppler technique, originally designed by Eik-Nes et al. (3) for volume blood flow calculations, was used. The results of the blood flow estimations are sensitive to several methodological errors, e.g. the ultrasound insonation angle, the vessel diameter measurement and the ultrasonic weight estimation. The waveform analysis is independent of those errors and offers additional information on fetal cardiovascular dynamics. The present longitudinal study describes the fetal aortic blood velocity waveform during the last trimester of normal pregnancy, whereas the volume blood flow was described in part I (13).

MATERIAL AND METHODS

Thirty-one pregnant women were examined every second week from the 27th gestational week till term. All women were healthy and their pregnancies uncomplicated on entering the study. However, the results

from 10 women had to be excluded as complications occurred later in their pregnancies. The combined 2 MHz pulsed Doppler and real-time ultrasound technique (4) was used for the fetal blood velocity measurements. The study group and the ultrasound technique were described in detail in part I (13).

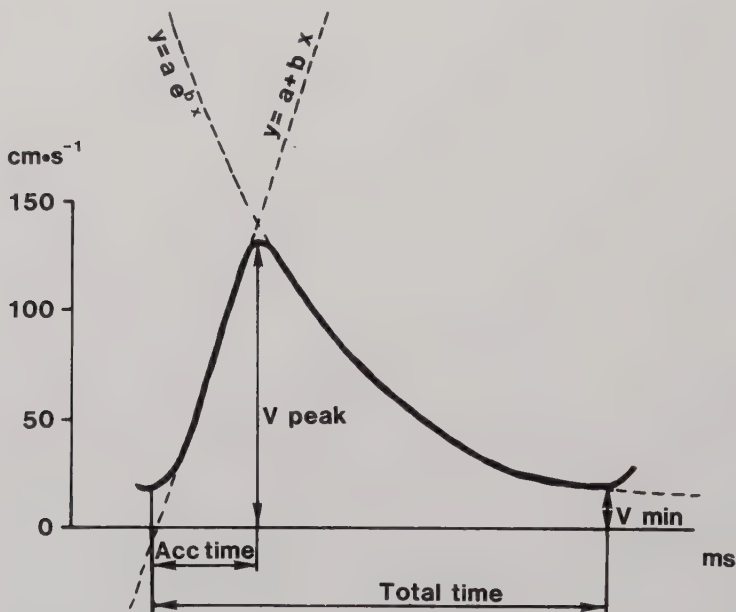


Figure 1. Schematic drawing demonstrating waveform analysis of the fetal aortic maximum blood velocity. V_{peak} = peak velocity; V_{min} = minimum velocity following the peak; Acc. time = acceleration time (start-to-peak time).

The blood velocity signals were recorded from the intermediate part of the descending thoracic aorta and from the abdominal aorta near the bifurcation. The maximum blood velocity, estimated from the Doppler shift spectrum by the automatic estimator built into the Doppler instrument (ALFRED, Vingmed A/S, Drammen, Norway), was used for the

waveform analysis. A spectrum analyser (DAISY, Vingmed A/S, Drammen, Norway) was used for the on-line quality control of the primary signals. Only signals recorded during periods of fetal quiescence, i.e. periods of fetal apnea and without fetal movements, were accepted for analysis.

The velocity traces were analysed by means of a digitizer and a microcomputer (ABC 806, Luxor, Motala, Sweden) with a curve-fitting program according to the least-square method. The velocity curve over the cardiac cycle was divided into two parts. The start of the blood velocity curve was defined as the point where the velocity curve turned to unbroken acceleration. The first part, the acceleration phase, was fitted to a linear function and the part following peak to an exponential function (Fig. 1).

TABLE I. Definitions of waveform parameters of the maximum blood velocity recorded from the fetal descending aorta.

Pulsatility index (PI)	$\frac{V_{\text{peak}} - V_{\text{min}}}{V_{\text{mean}}}$
Rising slope (RS) ($y=a+bx$)	$\frac{b}{V_{\text{mean}}}$
Descending slope (DS) ($y=ae^{-bx}$)	$\frac{b}{V_{\text{mean}}}$
Acceleration time	start to peak time
Acceleration time percentage	$\frac{\text{acceleration time}}{\text{total time}} \times 100$

V_{peak} = peak velocity, V_{min} = minimum velocity following the peak, V_{mean} = integrated mean velocity over the cycle. See also Fig. 1.

Table I describes the indices determined from the curve. The pulsatility index (PI) was defined according to Gosling et al. (7). The rising slope (RS) was defined as the acceleration during the first

part of the cycle normalized for the mean velocity over the cycle. The descending slope (DS) was extracted as the downward slope of the curve-fitted exponential function and was also normalized for the mean velocity over the cycle (15). Furthermore, the acceleration time and the percentual acceleration time proportion of the total cycle were calculated. All results were based on individual means of ten consecutive cardiac cycles. The intraindividual variability was evaluated by calculating the coefficient of variation

$$(CV = \frac{SD}{\text{mean}} \cdot 100).$$

For the PI in the fetal thoracic aorta, the mean CV was 6.9% (SD 3.9%).

The statistical analysis of the results was performed with the BMDP (Statistical Computer Programs, UCLA, Dept. of Biomathematics, California). Mean values, standard deviations (SD) and coefficients of correlation (r) were given. Intentionally, no p-values were presented, as the observations in the study were not independent and the correlation coefficients were used for descriptive purposes only.

RESULTS

All waveform parameters at both sites of measurement in the fetal aorta were independent of gestational age (Table II). The development of the PI and the RS during the observed period of pregnancy is presented in Fig. 2.

In the descending thoracic aorta, the correlation coefficient (r) between the peak maximum velocity and the fetal weight was -0.20. The RS was related to the acceleration time and to the peak velocity with coefficients of correlation -0.49 and 0.52, respectively. The DS correlated with PI (r=0.72) and with RS (r=0.52). The correlation coefficient between the PI and the RS was 0.61. The range of the fetal heart rate was 112 to 164 beats·min⁻¹. The relation of the acceleration time percentage, RS and PI to fetal heart rate is illustrated in Fig. 3. The correlation coefficients for the three parameters were 0.22, -0.10 and -0.43, respectively. The correlation coefficient

Table II. Correlation coefficient (r) with gestational age of waveform parameters characterizing fetal aortic blood velocity in 21 normal late pregnancies

	Descending aorta	
	Thoracic	Abdominal
V peak	-0.20	-0.27
V min	0.23	0.28
PI	0.15	0.22
RS	-0.22	-0.25
DS	-0.02	-0.21
Acceleration time	0.45	0.02
Acceleration time percentage	0.43	0.00

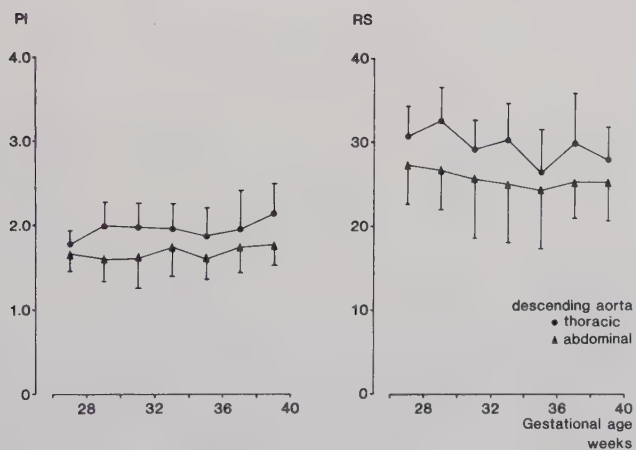


Figure 2. Pulsatility index (PI) and rising slope (RS) of the fetal aortic blood velocity waveform during the third trimester of normal pregnancy (means $\pm$ SD; $n=21$).

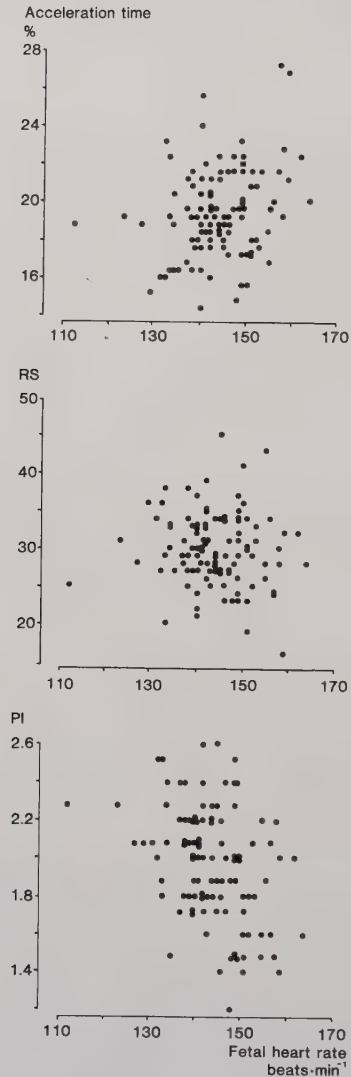


Figure 3. Waveform parameters of the maximum blood velocity recorded from the descending thoracic aorta plotted against fetal heart rate (n=21). RS = rising slope; PI = pulsatility index. For definitions see Table I.

between the peak maximum velocity and the fetal heart rate was -0.20.

In the abdominal aorta, the correlation coefficient (r) between the peak maximum velocity and the fetal weight was 0.27, between the RS and the acceleration time -0.41 and between the RS and the peak velocity 0.13. The DS correlated with PI ($r=0.69$) and with RS ($r=0.57$). The correlation coefficient between the PI and RS was 0.74. Correlation between the acceleration time percentage, RS, PI and the fetal heart rate had coefficients (r) 0.25, 0.05 and -0.22, respectively. For the peak velocity and the fetal heart rate the r was 0.04.

Typical waveforms of the maximum blood velocities recorded from the two fetal aortic sites are shown in Fig. 4.

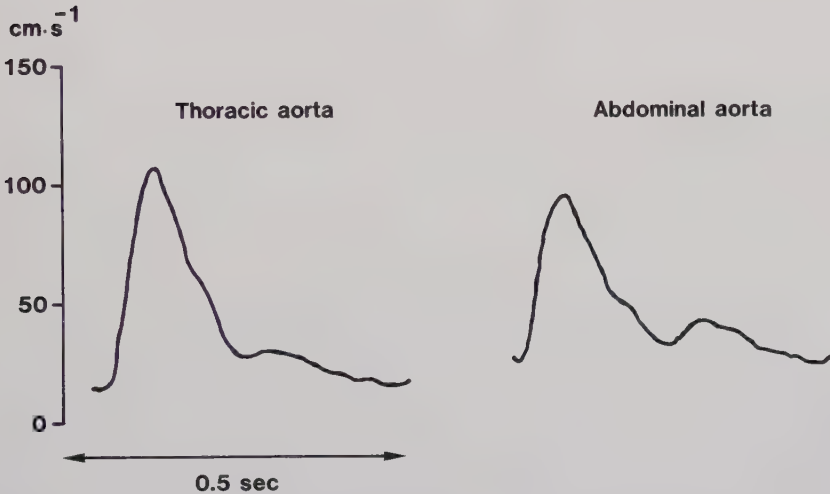


Figure 4. Typical traces of blood velocities recorded from the descending thoracic (left) and the abdominal (right) aorta of the fetus.

The descending thoracic aorta, higher systolic velocities and lower diastolic velocities were found than in the abdominal aorta. The mean values ($\pm$ SD) of the waveform parameters are given in Table III.

TABLE III. Mean values of waveform parameters characterizing fetal aortic blood velocity in 21 normal late pregnancies ($\pm$ SD)

	Descending aorta	
	Thoracic	Abdominal
V peak ($\text{cm}\cdot\text{s}^{-1}$)	115.6 $\pm$ 19.0	99.7 $\pm$ 18.8
V min ($\text{cm}\cdot\text{s}^{-1}$)	16.8 $\pm$ 4.9	18.6 $\pm$ 5.7
PI	1.96 $\pm$ 0.31	1.68 $\pm$ 0.28
RS	29.9 $\pm$ 4.9	25.7 $\pm$ 5.6
DS	5.3 $\pm$ 0.9	4.5 $\pm$ 0.9
Acceleration time (ms)	81.2 $\pm$ 10.0	82.1 $\pm$ 10.2
Acceleration time percentage	19.2 $\pm$ 2.2	19.1 $\pm$ 2.2

DISCUSSION

The fetal blood circulation was described as "hyperkinetic and low-resistant" (2). Due to the low peripheral vascular resistance in the placental circulation, the fetal aortic blood flow is characterized by a forward flow throughout the whole cycle, in contrast to the flow in the adult aorta (10).

Several investigators have presented waveform analyses of umbilical artery velocities (5,15, 16,18) showing waveform changes with progress of pregnancy, which indicated a subsequent lowering of the peripheral resistance of the placental vascular bed. This was reflected by the increasing diastolic proportion of flow, decreasing peak to minimum velocity ratio (A/B ratio) and decreasing PI (16).

Gosling et al. (7) stated that the PI increases with increasing peripheral resistance. The umbilical artery velocity waveform reflects

mainly the placental vascular resistance and its PI increases in cases with placental insufficiency (16). Jouppila et al. (11) claimed that waveform changes in growth retarded fetuses appear early in the fetal aorta as an expression of peripheral vasoconstriction within the fetus. The waveform of the aortic blood velocity is probably more sensitive to cardiovascular compensatory mechanisms e.g. blood flow redistribution, than the waveform of velocity obtained from the umbilical arteries. The indices of peripheral vascular resistance in the fetal descending thoracic aorta are affected by the resistance in the visceral vascular bed, in the lower extremities and in the placenta, while the same parameters in the distal abdominal aorta are affected by the vascular resistance in the lower extremities and the placental bed only.

Griffin et al. (8) found that the fetal aortic end-diastolic velocity increases with gestational age. In our study, somewhat higher diastolic velocities were seen in the abdominal than in the thoracic aorta, although the variation was large (Table III). These findings may suggest a lower peripheral resistance distally than proximally in the aorta, probably due to the nearness to the placental vascular bed. As demonstrated in part I (13), the placental proportion of the aortic flow diminished while the proportion of flow to viscera and lower extremities increased with increasing length of gestation. These proportional changes of the flow distribution probably influenced the appearance of the velocity waveform in the abdominal aorta and thereby also the PI.

Stuart et al. (18) suggested that the acceleration slope of the umbilical arterial blood velocity mainly reflects cardiac performance. The latter, however, can probably better be judged on from measurements performed close to the fetal heart. Alverson et al. (1) found a close relation between myocardial contractility and the aortic blood acceleration in experiments in the adult dog. These results were consistent with our own study performed on the thoracic descending aorta of exteriorized fetal lambs, as long as the peripheral resistance was unaffected (14).

Wladimiroff et al. (19) and Jouppila et al. (11) used waveform analysis of the mean Doppler frequency shift recorded from the fetal aorta. We considered the maximum frequency shift to be more sensitive to changes in the haemodynamics than the mean Doppler shift frequency, and less sensitive to errors, e.g. interference with flow in nearby lying vessels and localization of sample volume over the vessel. The estimated mean blood velocity is also more sensitive to various flow profiles in the vessel and to the filtering of the signals than is the maximum velocity. Under normal circumstances (uncompromized fetal circulation, insonation angle 45°) the maximum velocity recording is not affected by the high-pass filtering and the mean blood velocity is only slightly affected (6). However, in cases with impaired circulation, e.g. in growth retarded fetuses, in which the diastolic velocities are decreased (8,11,12), the mean blood velocity signals will be highly affected by the high-pass filter as the mean velocity in the diastolic part of the cycle reaches the filter's cut-off level earlier than does the maximum velocity. The former is then erroneously recorded as zero velocity in spite of possibly still existing forward flow. These arguments made us decide to use the maximum velocity for the waveform analysis.

There are, however, possible errors connected even with the blood velocity waveform recording and analysis. One major source of error in the present set-up is the interference with blood flow in a nearby vessel. This is controlled and avoided by means of an on-line spectrum analysis and audial control of the primary signals and by the use of pulsed Doppler technique for an adequate depth resolution. Another source of possible error in connection with the off-line waveform analysis is the definition of the start of each cycle. The start point might be defined as the point marking the end of the deceleration phase and beginning of the acceleration phase. However, this point is sometimes the false start of the acceleration phase of the beat, as oscillations in the diastole of the preceding beat can sometimes occur. We tried to avoid this uncertainty by defining the start of the acceleration phase visually on the velocity trace as the point where the blood flow starts its unbroken acceleration.

In the present study, the statistics (mean, SD, r) were used for the description of the results only. This because the statistical interpretation of p -values in longitudinal studies with dependent observations is not obvious (P.-E. Isberg, personal communication).

The acceleration time percentage, RS and PI did not show any strong relation to fetal heart rate or to gestational age, which justifies the use of the gestational age-independent reference values in the fetal aorta for the last 3 months of gestation, at least within the normal fetal heart rate range.

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Haemodynamic assessment of fetal heart arrhythmias

GÖRAN LINGMAN, JAN-ANDERS DAHLSTRÖM, STURLA H. EIK-NES, KAREL MARŠÁL, PER OHLIN & STEN OHRLANDER *Departments of Obstetrics and Gynaecology, University Hospital, Malmö and Central Hospital Helsingborg, and the Department of Clinical Physiology, Central Hospital, Helsingborg, Sweden*

Summary. The effects of fetal heart arrhythmias were examined serially in two pregnancies by three non-invasive methods: fetal ECG, fetal phonocardiography and ultrasonic measurement of fetal blood flow. In a case of supraventricular arrhythmia, there was evidence suggesting that the stroke volume varied with ventricular filling according to the Frank-Starling law. In a case of total atrioventricular block the mean blood flow in the fetal descending aorta and in the umbilical vein was within the normal range. Blood flow velocity in the inferior vena cava of the fetus reflected atrial contractions. In the phonocardiogram, a phenomenon similar to 'bruit de canon' was found. Both pregnancies had good outcomes and subsequent development of the infants was normal except for the persisting dysrhythmias. The two cases exemplify how fetal heart function can be assessed *in utero*.

Irregular fetal heart sounds are accidentally heard at antenatal examinations and doubts may arise about their significance. Fetal heart arrhythmias have been considered a sign of immaturity of the conducting system without clinical importance (Levkoff 1969), but certain arrhythmias, such as paroxysmal supraventricular tachycardia and bradycardia can have severe haemodynamic consequences (Silber & Durnin 1969; Schreiner *et al.* 1978; Valerius *et al.* 1978; Lingman *et al.* 1980). Therefore, it is of interest to assess the haemodynamic effects of heart arrhythmias. The present paper exemplifies such assessment with non-invasive methods in two patients with severe fetal heart rhythm disturbances.

Methods

Abdominal fetal ECG was recorded with a commercial electrocardiograph with an additional amplifier (Siemens-Eléma, Stockholm, Sweden). During labour and delivery, direct fetal ECG was registered from the fetal scalp. Simultaneously

with the abdominal fetal ECG, fetal phonocardiogram was recorded by means of a microphone (Siemens-Eléma, Stockholm, Sweden) located over the fetal heart.

Blood flow in the fetal descending aorta, intra-abdominal part of the umbilical vein and inferior vena cava of the fetus was measured transcutaneously by a method combining real-time ultrasonography with pulsed Doppler ultrasound (Eik-Nes *et al.* 1982). The pulsed Doppler velocity meter (Alfred, Vingmed A/S, Oslo, Norway) automatically analysed the Doppler shift frequency spectrum to give estimates of mean and maximum blood flow velocity output signals. The diameter of the vessel was measured directly on the real-time ultrasound image (ADR, Tempe, Arizona, USA). From the estimated values of the mean blood flow velocity and the vessel diameter, fetal blood flow was calculated.

Clinical information and results

Patient no. 1

A 32-year-old healthy woman, who had borne two children, was referred in the 25th week of pregnancy because of fetal bradycardia. At the first examination, irregular fetal heart sounds with

*Correspondence: G. Lingman, Department of Obstetrics and Gynaecology, University Hospital, S-214 01 Malmö, Sweden.

alternating periods of tachycardia and bradycardia were heard. Fetal haemodynamics were then assessed every second week on an out-patient basis. Fetal heart anatomy was normal and no signs of fetal cardiac insufficiency such as heart enlargement, ascites or hydrothorax were shown at repeated ultrasound examinations.

Clinical examination remained normal. The fetal heart arrhythmia persisted throughout the pregnancy. At 39 weeks gestation, labour started spontaneously. The fetal bradycardia impaired the value of CTG as an indicator of fetal distress during labour. Analyses of pH in fetal scalp blood samples gave normal values. A girl weighing 2910 g was delivered after 4.5 h labour without signs of fetal distress (Apgar scores of 8 and 10 at 1 and 5 min respectively). Echocardiography postpartum confirmed normal heart anatomy. In the neonatal period, episodes of supraventricular tachycardia alternating with episodes of bradycardia occurred. Treatment with digitalis and propranolol was started in the neonatal period to prevent heart failure and recurrent tachycardia. After 2 months, the child had a normal sinus rhythm. After 6 months the treatment was stopped. A 2-year follow-up revealed normal development and a normal heart action.

Fetal electrocardiograms were recorded nine times between the 25th and 40th weeks of pregnancy. In the five ECGs before the 32nd week, periods of regular bradycardia with a frequency of 85 to 90 beats/min and periods of tachyarrhythmia with a frequency >200 beats/min were present. After the 32nd week periods of regular rhythm and frequent supraventricular extrasystoles were recorded. The basal frequency ranged from 95 to 140 beats/min. During the first stage of labour supraventricular bradycardia (60–95 beats/min) with frequent nodal extrasystoles was recorded. Long periods

of supraventricular tachycardia (210 beats/min) occurred 30 min before delivery. Then the rhythm switched to sinus bradycardia and, immediately before delivery, to nodal rhythm with a ventricular frequency of 60 beats/min. During the neonatal period an ECG pattern of irregular heart rhythm was recorded with paroxysmal tachycardia (200–210 beats/min) alternating with frequent blocked supraventricular extrasystoles resulting in ventricular bradycardia (95 beats/min).

Fetal phonocardiograms were registered from the 33rd gestational week until birth. Fig. 1 shows a phonocardiogram in the 33rd week of pregnancy with a rate of 96/min with the beats grouped in pairs. In the second beat of each pair a short murmur occurred in the 50-Hz frequency band.

Ultrasonic measurement of fetal aortic blood flow was performed in the 32nd, 36th and 38th week of gestation. The peak maximum velocity values were related to the preceding beat-to-beat intervals (Fig. 2). After a long beat-to-beat interval (660–730 ms), the peak maximum velocity was significantly higher than during periods of tachycardia (160 beats/min).

In the 32nd and 36th week of pregnancy, spectral analysis of the Doppler shift signals revealed a consistent spike of short duration just before, or in the second beat during the periods of coupled beats. The peak velocity of these spikes was approximately half the values of the second beat's peak (Fig. 3). The spikes coincided with the murmur recorded in the phonocardiogram in the 33rd week (Fig. 1).

A simultaneous recording of fetal ECG and fetal aortic blood flow showed that the second beats in the pairs were followed by incomplete compensatory pauses and had QRS complexes which were broader than those of the first normal

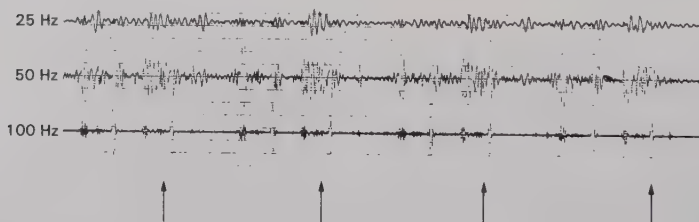


Fig. 1. Fetal phonocardiogram in the 33rd week of pregnancy (patient no. 1). Arrows indicate a systolic murmur in the 50-Hz frequency band.

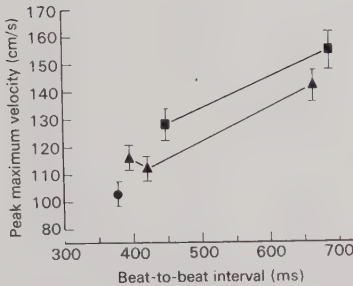


Fig. 2. Ultrasonically measured peak maximum velocity of the fetal aortic blood flow related to the preceding beat-to-beat interval (patient no. 1, 36th week of pregnancy, mean $\pm$ SD). ●, Period of regular tachycardia; ■, period with beats grouped in pairs; ▲, period with beats coupled in groups of three.

beats. During periods of regular rhythm no additional spikes were observed in the Doppler spectrum. In the neonatal period, the phonographically registered murmurs did not occur.

Patient no. 2

A 30-year-old healthy woman had previously been delivered by caesarean section because of a relatively narrow pelvis and breech presentation. She was referred to the ultrasound laboratory when fetal bradycardia was heard at 25 weeks gestation. The ultrasound verified ventricular bradycardia (56 beats/min) with atrioventricular dissociation. There were no signs of fetal heart

insufficiency and the fetal heart anatomy was normal. The subsequent clinical course was normal but the ventricular bradycardia and the atrioventricular dissociation persisted throughout the pregnancy. Maternal serology for connective tissue diseases was negative. At 39 weeks gestation, the patient was delivered by an elective caesarean section because of her obstetric history. The female infant weighed 2750 g and showed no signs of heart insufficiency, she did not require treatment, even though the total atrioventricular block (AV-block) persisted. Further development of the child was normal. At the age of 1 year, the circulation was fully satisfactory.

Recordings of fetal ECG were attempted every second week from the time the bradycardia was diagnosed, but were not of adequate quality until after the 33rd week. They then confirmed ventricular bradycardia of 56 beats/min.

The fetal phonocardiogram remained unchanged from the 25th week until delivery showing a constant regular bradycardia of 56 beats/min. The amplitude of the first heart sound varied (Fig. 4) in a manner suggesting a 'bruit de canon'. This is observed in cases of AV-block because of ventricular contractions at varying degree of closure of the atrioventricular valves (Strandell 1967).

Fetal blood flow velocity was measured in the 34th, 36th and 38th weeks of gestation. The results are summarized in Table 1. The values of the aortic and umbilical blood flow were within the normal range (Eik-Nes *et al.* 1981). Blood flow velocity tracings in the inferior vena cava showed negative modulations with a frequency of

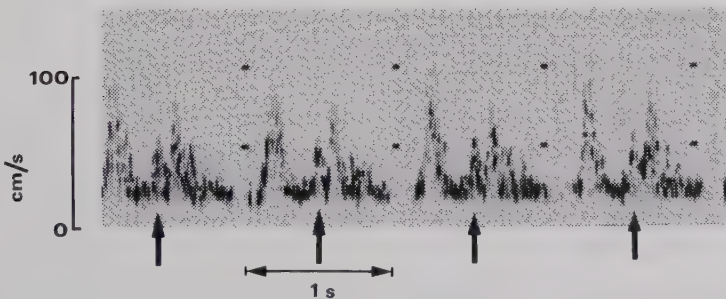


Fig. 3. Spectral analysis of the Doppler signals from the fetal aortic blood flow (patient no. 1, 36th week of pregnancy). The beats are grouped in pairs; an additional spike (marked by an arrow) appeared in the second beat of each pair.

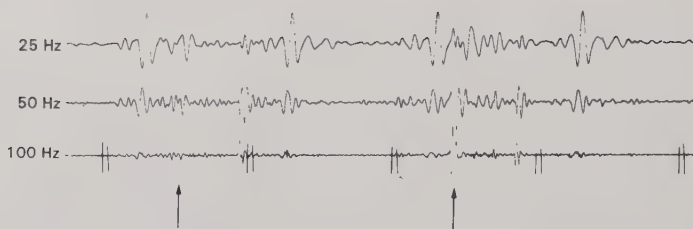


Fig. 4. Phonocardiogram of a fetus with total atrioventricular block (patient no. 2, 33rd week of pregnancy). The first heart sound signals marked by arrows show varying amplitude: the high amplitude sounds correspond to the 'bruit de canon'.

126 beats/min reflecting atrial contractions and confirming the AV-block (Fig. 5).

Discussion

Most fetal arrhythmias are quite harmless, but some can lead to severe cardiac insufficiency and possibly even to intrauterine death. Therefore, there is a need for identification of the arrhythmia and for assessment of its haemodynamic effects (Shenker 1979). Fetal ECG identifies the type of arrhythmia when recordings of good quality are obtained. However, during the second half of pregnancy, it is sometimes impossible to record abdominal fetal ECG signals (Wheeler *et al.* 1979). Fetal M-mode echocardiography can be a useful tool in such instances (Kleinman *et al.* 1983). The ultrasonic examination of the fetal

blood flow (Eik-Nes *et al.* 1982) might facilitate the classification of the arrhythmia and enables the quantitative evaluation of its effects on the fetal haemodynamics. In the present paper we describe the examinations of two cases with severe fetal arrhythmias using abdominal fetal ECG, fetal phonocardiogram and ultrasonic measurement of the fetal blood flow.

Blood flow measurements showed that an increased beat-to-beat interval is followed by a higher peak maximum velocity in the descending fetal aorta (Fig. 2). The maximum velocity of the aortic blood flow reflects the stroke volume (Hatle & Angelsen 1981). Therefore the present finding suggests an increased stroke volume after a prolonged ventricular filling phase with higher end-diastolic volume according to the Frank-Starling law. This supports the reports by Kirkpatrick *et*

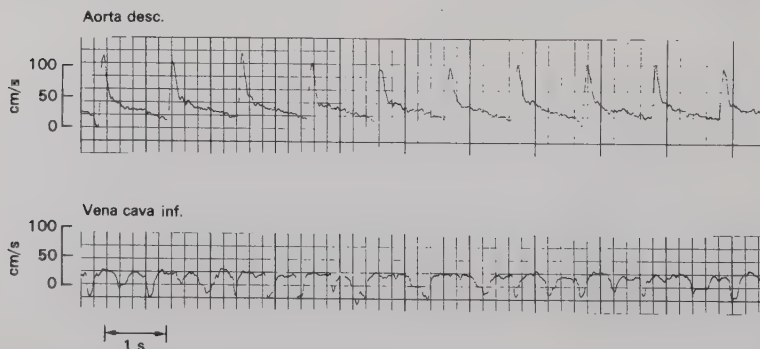


Fig. 5. Analogue signals of the mean blood flow velocity in the descending aorta (upper trace) and inferior vena cava (lower trace) of the fetus with the atrioventricular dissociation (patient no. 2, 36th week of pregnancy). Aortic pulsations reflect the ventricular function (56 beats/min); pulsatory modulations of the blood flow in the inferior vena cava reflect the atrial contractions (126/min).

Table 1. Results of the blood flow measurements in the fetus with a total AV-block (case no. 2)

Fetal blood flow measurement	Gestation (weeks)		
	34	36	38
Descending aorta			
Mean velocity (cm/s)	24	23	21
Peak maximum velocity (cm/s)	101	86	95
Mean blood flow (ml/min/kg)	235	209	203
Umbilical vein			
Mean velocity (cm/s)	—*	13	16
Mean blood flow (ml/min/kg)	—*	124	115

*Interference with fetal breathing movements.

al. (1976) and Anderson *et al.* (1980) who stated that the fetal stroke volume is increased by augmented ventricular filling. This is in contradiction to the previous opinion that the fetal cardiac output can be increased by higher heart frequency only (Rudolph & Heymann 1974).

In the periods of coupled beats in patient no. 1 spectral analysis of the Doppler shift frequencies showed spikes of uncertain origin in the second beat. These spikes and the coinciding murmurs, registered in the second beats, might be due to bundle-branch blocked supraventricular extrasystoles with a changed pattern of myocardial contraction.

In patient no. 2, a pulsatile fetal aortic blood flow with a frequency of 56/min was registered, while in the inferior vena cava negative pulses at 126/min were detected. This confirms the AV-dissociation and proves also that the pulsations, recorded in the inferior vena cava during fetal apnoea are retrograde and due to the atrial contractions and not to the transmission of the aortic pulses.

A detailed ultrasonic examination is essential for excluding possible congenital cardiac abnormality as the cause of the fetal arrhythmia. In our patients, the fetuses had normal cardiac anatomy and no signs of cardiac insufficiency, such as ascites, hydrops and heart enlargement. The blood flow values were within the normal range in spite of the severe arrhythmias.

Fetal ECG and phonocardiography in combination with ultrasonic blood flow measure-

ments offer help in the prenatal classification of the fetal heart arrhythmias. The fetal blood flow measurements allow the haemodynamic effects of the arrhythmia to be assessed. These may be also used to evaluate possible intrauterine pharmacological therapy (Lingman *et al.* 1980) and to assess the timing of delivery.

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CIRCULATORY EFFECTS OF FETAL HEART ARRHYTHMIA

Göran Lingman, M.D. and Karel Maršál, M.D., Ph.D.

Department of Obstetrics and Gynecology, General Hospital, University
of Lund, Malmö, Sweden

ABSTRACT

The circulatory effects of fetal heart arrhythmia were studied in utero in 37 late pregnancies. A combined real-time linear array and 2 MHz pulsed Doppler technique was used for blood flow estimation and waveform analysis of the maximum blood velocity recorded from the thoracic descending aorta of the fetuses. Blood velocity recordings from the inferior vena cava reflected fetal atrial contractions, while the aortic blood velocity represented the ventricular activity. Analysis of the traces from the two fetal vessels facilitated the classification of the arrhythmias into three main groups: supraventricular arrhythmia (n=29), atrioventricular block (n=5) and ventricular arrhythmia (n=3). Blood flow in the thoracic descending aorta was normal in all fetuses but one. This fetus had an atrioventricular block with concomitant heart malformation and an aortic blood flow of $77 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. It died in utero with signs of heart failure. The pulsatility index of the aortic blood velocity was not significantly altered in any of the arrhythmia groups. The peak blood velocity, the rising slope and the blood acceleration were increased in the beats following a prolonged ventricular filling time, i.e. in the postextrasystolic beats and in atrioventricular block. Conversely, the corresponding values were lower in the extrasystolic beats and in tachycardia. The study demonstrated the ability of the fetal heart to maintain adequate circulation despite a severe arrhythmia. Furthermore, the results support the opinion that the Frank-Starling's law is valid also for the fetal myocardium.

INTRODUCTION

Auscultation of fetal heart sounds has been used for many years in clinical obstetrics as a method of monitoring fetal well-being. Sometimes, irregular fetal heart action is heard, but until recently, it was impossible to judge the effects of the cardioarrhythmia on the fetal circulation. Ultrasonography in its time-motion mode made possible intrauterine study of fetal heart dynamics¹ and was applied to fetuses having heart arrhythmia.^{2,3}

Combination of two-dimensional real-time ultrasonography and pulsed Doppler technique made possible non-invasive evaluation of fetal hemodynamics by quantifying fetal aortic blood flow^{4,5} and by analyzing the waveform of the aortic maximum blood velocity.⁶ The suitability of the method for the study of fetal cardiac arrhythmia was suggested recently.^{2,5,7,8,9} In the present investigation, the hemodynamic consequences of various types of fetal arrhythmia were examined.

MATERIAL AND METHODS

The study group comprised 37 healthy pregnant women who were referred to our ultrasound laboratory because of irregular fetal heart sounds. Median age of the women was 28 years (range 19 to 43 years); 17 women were primiparae and 20 multiparae. Median gestational age at the time of examination was 34 completed weeks (range 22 to 40 weeks). All pregnancies but one were ultrasonically dated before the 20th gestational week. Median pregnancy length at delivery was 40 weeks (range 35 to 42 weeks). Thirty-two women were delivered vaginally and five by means of cesarean section. The indications for cesarean sections were in two cases fetal tachycardia with imminent heart failure; in one, fetopelvic disproportion; in one, maternal bronchial asthma; and in one, fetal distress in labor. Nineteen newborns were females and 18 were males. Median birth weight was 3,380 g (range 1,600 to 4,610 g). Of the liveborn neonates, 31 had an Apgar score ≥ 8 at 1 min and ≥ 9 at 5 min, 3 had an Apgar score ≤ 7 at 1 min, and > 8 at

5 min, and 2 $\leq$ 7 both at 1 and 5 min. One fetus died in utero after 42 postmenstrual weeks.

A 2 MHz pulsed Doppler instrument (ALFRED, Vingmed A/S, Horten, Norway) with a 100 Hz high-pass filter was utilized for the fetal blood velocity measurements. The Doppler transducer was attached to the real-time linear array transducer (ADR 2130, Advanced Diagnostic Research Corp., Tempe, Arizona) at a fixed angle of 45° , thus making possible correction of the mean blood velocity for the insonation angle.¹⁰

Recordings of the fetal blood velocity were performed in the inferior vena cava (IVC) and in the thoracic descending aorta. Only recordings performed during fetal apnea were accepted. The aortic diameter was measured by means of a Time-Distance recorder¹¹ connected to the real-time scanner. From the values of the mean velocity and the mean diameter, fetal aortic blood flow was calculated and expressed in $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. In cases of regular tachycardia and atrioventricular block, the average aortic stroke volume ($\text{ml} \cdot \text{kg}^{-1}$) was calculated by dividing the mean blood flow by the heart rate. A waveform analysis of the maximum aortic blood velocity was performed off-line using a digitizer and a microcomputer (ABC 806, Luxor, Motala, Sweden).⁶ The rising slope (RS), acceleration time, acceleration time percentage, peak velocity and pulsatility index (PI)¹² were used to characterize the waveform (Fig.1). The results from periods of arrhythmia were compared with those from periods of regular rhythm in the same fetus at the same examination (at least 5 consecutive beats) and with normal values.^{6,13}

Aortic pulses reflecting ventricular contractions, and deflections in the IVC blood velocity reflecting atrial contractions, were the basis for the classification of the arrhythmia. Three groups of arrhythmia were identified: supraventricular arrhythmia (including extrasystoles, missed beats, and tachycardia), atrioventricular block, and ventricular extrasystoles. Four fetuses had various types of supraventricular arrhythmia at different examinations and are represented in several subgroups.

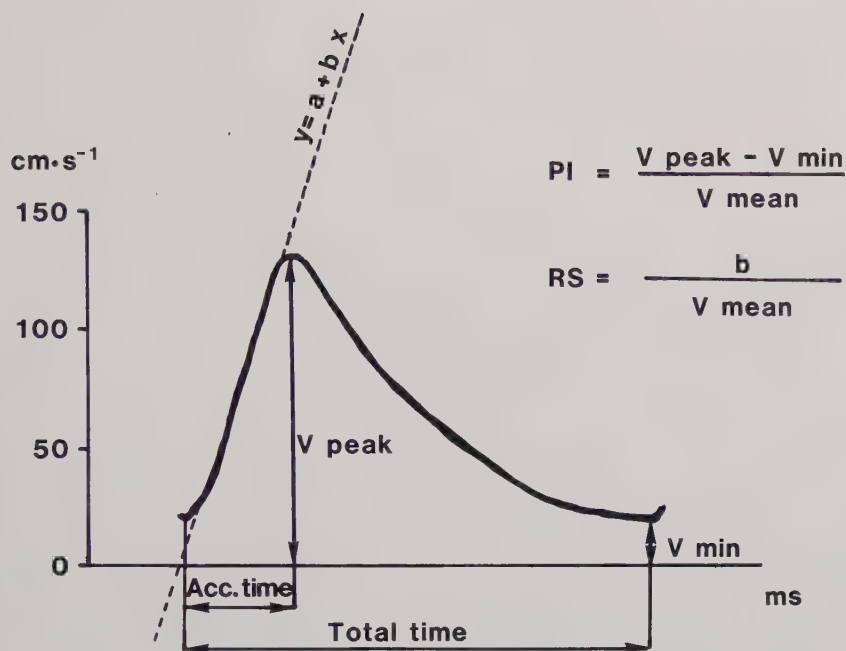


Figure 1. Schematic drawing demonstrating waveform analysis of the fetal aortic maximum blood velocity. Vpeak = peak velocity; Vmin = minimum velocity following the peak; acc. time = acceleration time (start-to-peak time). PI = pulsatility index; RS = rising slope; Vmean = mean velocity over the cycle.

The results were statistically evaluated with Student's t-test for paired observations, t-test for two means and linear regression analysis. $p=0.05$ was accepted as the level of significance. For groups comprising less than 6 fetuses, no statistical evaluation was attempted.

TABLE 1. Aortic blood velocity waveform parameters in 20 fetuses with single supraventricular extrasystoles.

	Pre-extra- systolic beat		Period of arrhythmia Extrasystole		First postextra- systolic beat	Period of regular rhythm	Normal values
V _{peak} (cm·s ⁻¹)	Mean	107.1	76.8	123.0	108.6	115.6	
	+ SD	+20.4	+25.2		+19.8	+19.0	
	Signifi- cance of difference	p<0.05	p<0.001	p<0.001	p<0.001		
Rising slope	Mean	23.1	21.3	27.9	25.7	29.9	
	+ SD	+8.1	+10.7	+ 6.9	+ 6.1	+ 4.9	
	Signifi- cance of difference	p<0.001	p<0.001	p<0.01	p<0.05		
Accelera- tion (cm·s ⁻²)	Mean	1305	695	1519	1234	1514	
	+ SD	+434	+339	+447	+307	+292	
	Signifi- cance of difference	p<0.001	p<0.001	p<0.001	p<0.05		
Accelera- tion time percentage	Mean	26.3	19.4	21.6	20.7	19.2	
	+ SD	+6.3	+ 7.5	+3.8	+2.8	+2.2	
	Signifi- cance of difference	n.s.	n.s.	n.s.	n.s.		
Pulsatility index	Mean	1.42	2.07	1.97	1.75	1.96	
	+ SD	+0.49	+0.89	+0.43	+0.28	+0.31	
	Signifi- cance of difference	n.s.	n.s.	n.s.	n.s.		

RESULTS

Supraventricular arrhythmia

Single extrasystoles (Table I)

Twenty fetuses had premature atrial contractions reflected in the IVC as velocity deflections, often negative (Fig. 2) and in the descending aorta as extrasystolic pulses (Fig. 3). The peak aortic velocity of the first postextrasystolic beat was higher ($p < 0.001$) than the average peak velocity in a period of regular rhythm in one and the same fetus (Fig. 3). It was also higher than the peak velocity of the beat immediately preceding the extrasystole ($p < 0.05$) and of the extrasystolic beat ($p < 0.001$). The RS of the first postextrasystolic beat was higher than the RS of the beat preceding the extrasystole ($p < 0.001$) and the RS of the regular beats ($p < 0.05$).

cm · s⁻¹

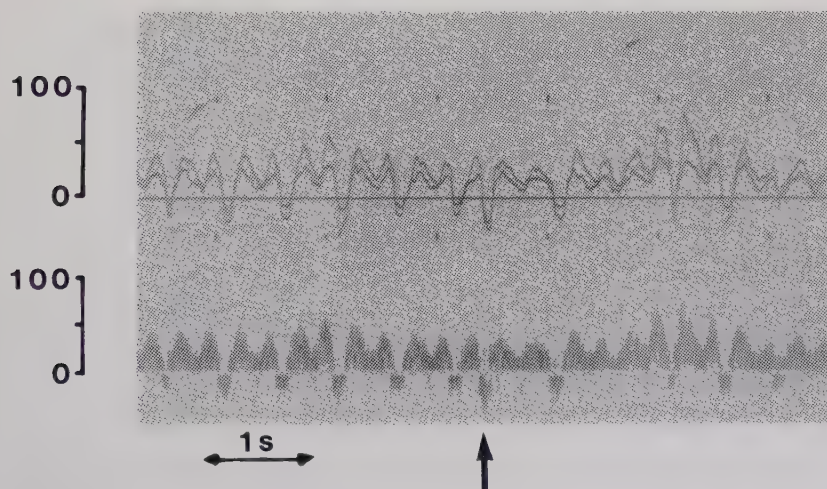


Figure 2. Premature atrial contraction (arrow) reflected in the blood velocity signals recorded from the fetal inferior vena cava. Doppler shift spectrum in the lower part; analogue signals of the estimated maximum and mean velocity in the upper part.

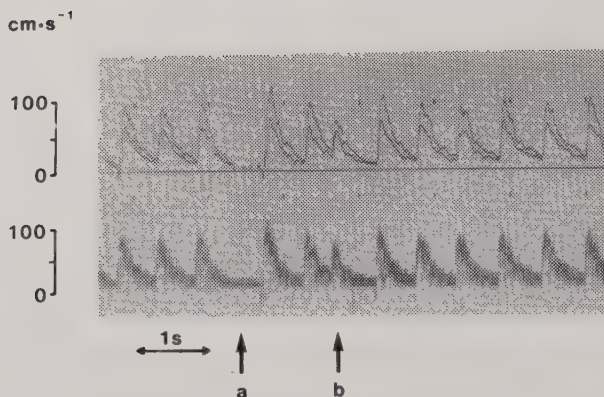


Figure 3. Blood velocity signals recorded from the descending thoracic aorta of a fetus with supraventricular extrasystoles. The extrasystoles are recorded as a missing beat (arrow a) and an extrasystolic beat (arrow b). Doppler shift spectrum in the lower part, analogue signals of the estimated maximum and mean velocity in the upper part.

The systolic acceleration of the extrasystolic beat was lower than the acceleration of the preceding beat ($p < 0.001$), the postextrasystolic beat ($p < 0.001$), and of the regular beats ($p < 0.001$). There were no differences in the acceleration percentage time between the various types of beat. The same was true for the PI.

The peak maximum velocity (Fig. 4), the RS, and the systolic acceleration of the extrasystolic and the first postextrasystolic beat were significantly correlated to the preceding beat-to-beat intervals, with correlation coefficients (r) 0.67 ($p < 0.001$), 0.60 ($p < 0.001$), and 0.51 ($p < 0.05$), respectively.

Neither the time-averaged aortic mean blood velocity ($32.0 \text{ cm} \cdot \text{s}^{-1}$, SD 4.8) nor the aortic blood flow (mean $249.6 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, SD 54.3) differed from the normal material ($34.6 \text{ cm} \cdot \text{s}^{-1}$, SD 5.5, and $231.7 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, SD 44.6, respectively).

Two fetuses had cardiac malformations (one had a ventricular septum defect and one a double outlet ventricle, pulmonary valve stenosis, ventricular septum defect and a vessel transposition). The blood flow values and the waveform parameters in these two fetuses did not differ from the rest of the group.

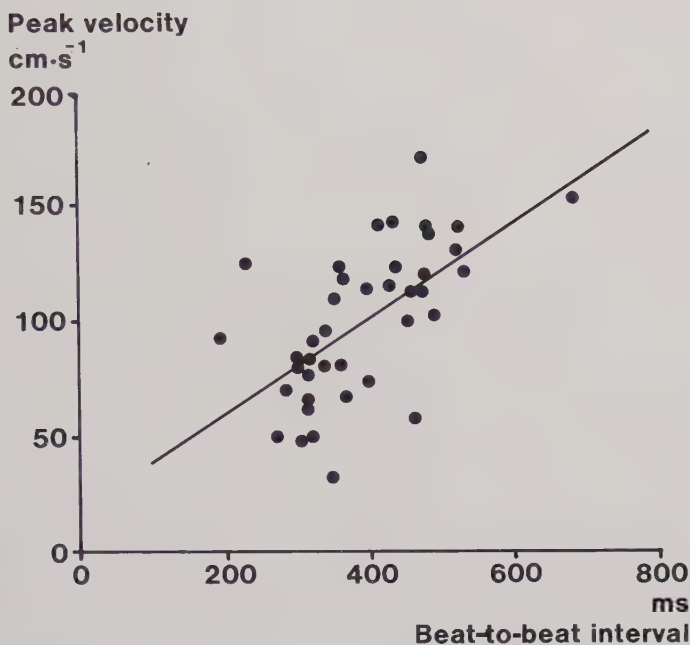


Figure 4. Peak maximum velocity ($\text{cm}\cdot\text{s}^{-1}$) plotted against the preceding beat-to-beat interval (ms) with regression line ($y = 18.91 + 0.21x$). Coefficient of correlation $r=0.67$ ($p<0.001$).

Extrasystoles in trigeminy (Table II)

Three fetuses evidenced long periods of atrial extrasystoles occurring every third beat. Corresponding to the extrasystoles, beats were missing in the aorta. The peak velocity was higher in the first than in the second postextrasystolic beat in all 3 cases. The RS was lower in the beat after the compensatory pause than in the following coupled beat. The time-averaged mean blood velocity (mean $28.7 \text{ cm}\cdot\text{s}^{-1}$, SD 1.4) and blood flow ($220.6 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$, SD 8.5) did not differ from the normal material.

TABLE II. Aortic blood velocity waveform parameters in fetuses with supraventricular arrhythmia - missed beats, extrasystoles in trigeminy and tachycardia.

	Missed beats (n=6)			Extrasystoles in trigeminy (n=3)			Tachycardia (n=4)	Normal values
	First beat after pause	Period of regular rhythm	Fetus no.	First post- extrasysto- lic beat	Second post- extrasysto- lic beat			
Vpeak (cm·s ⁻¹)	Mean	122.5	1	135.7	117.1		71.4	115.6
	+SD	+20.4	2	123.5	109.6		+7.9	+19.0
	Signifi- cance of difference	p<0.05	3	140.0	127.9			
Rising slope	Mean	29.2	1	31.3	63.7		25.5	29.9
	+SD	+9.7	2	26.9	33.0		+5.1	+4.9
	Signifi- cance of difference	n.s.	3	16.4	36.7			
1514 Accel- eration (cm·s ⁻²)	Mean	1422	1	1775	2051		924	
	+SD	+497	2	1504	1238		+116	+292
	Signifi- cance of difference	n.s.	3	1010	1585			
Accel- eration time per- centage	Mean	22.5	1	21	9		26.9	19.2
	+SD	+3.7	2	20	13		+2.0	+2.2
	Signifi- cance of difference	n.s.	3	28	10			
Pulsa- tility index	Mean	2.37	1	2.08	4.00		1.56	1.96
	+SD	+0.58	2	1.84	2.65		+0.36	+0.31
	Signifi- cance of difference	n.s.	3	1.76	2.04			

Missed beats (Table II)

Six fetuses had missed beats, which could also be defined as sinus arrest as no atrial contractions were seen in the IVC velocity traces. The first aortic beat after the pause had a higher peak velocity than the beats in the reference period ($p < 0.05$). No other differences in the waveform parameters were found. The time-averaged mean aortic blood velocity (mean $30.1 \text{ cm} \cdot \text{s}^{-1}$, SD 3.2) and the blood flow (mean $242.8 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, SD 57.7) were within normal limits.

Three fetuses showed signs of fetal distress during labor (one had an Apgar score 3 at 1 min, 7 at 5 min, and 9 at 10 min; one had meconium-stained amniotic fluid and one had an umbilical venous pH of 6.99; the latter two fetuses had normal Apgar scores). The three babies recovered quickly after birth.

Tachycardia (Table II)

Supraventricular tachycardia was found in 4 fetuses. The aortic pulse frequency ranged between 200 and $238 \text{ beats} \cdot \text{min}^{-1}$. The peak velocity, the systolic acceleration and the RS were lower and the acceleration time percentage higher than in the normal material. The time-averaged mean blood velocity ($25.6 \text{ cm} \cdot \text{s}^{-1}$, SD 5.1 cm) and the blood flow ($209.5 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, SD, 11.2 ml) were within normal range. The average aortic stroke volume was $0.96 \pm 0.09 \text{ ml} \cdot \text{kg}^{-1}$ (in the normal material with heart frequency 110-180 $\text{beats} \cdot \text{min}^{-1}$ a corresponding value was $1.74 \pm 0.32 \text{ ml} \cdot \text{kg}^{-1}$).

In 2 cases the tachycardia turned spontaneously to normal rhythm in utero. In one of these cases the mother was using cannabis during the time the fetal tachycardia was present. After she stopped this drug abuse the rhythm of the fetal heart normalized. One woman underwent a cesarean section at another hospital after 35 weeks of pregnancy due to persistent fetal tachycardia with increasing width of the fetal IVC. The heart frequency normalized within 2 days following birth.

Atrioventricular block (Table III)

A grade III atrioventricular block was found in 5 cases. The results in one case are not included in Table III as the fetus was in an unstable circulatory condition and died in utero within 12 hours. In all 5 fetuses, dissociation of the atrial and ventricular contractions was demonstrated in the real-time ultrasound image. Furthermore, pulsations with frequencies of normal fetal heart rate ($120-160 \text{ beats} \cdot \text{min}^{-1}$) were detected in the IVC, while the aortic pulse frequency ranged between 53 and 73 $\text{beats} \cdot \text{min}^{-1}$.

In the 4 fetuses described in Table III the peak velocity, the systolic acceleration, and the PI were all higher than in the normals. The acceleration time percentage was lower than normal. The time-averaged mean blood velocity (mean $29.2 \text{ cm} \cdot \text{s}^{-1}$, SD 8.9) and blood flow (mean $227.9 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$, SD 38.2) were within the normal range. The aortic stroke volume was $3.57 \text{ ml} \cdot \text{kg}^{-1}$ (SD 0.59) which is above the normal range.

In one fetus the bradycardia turned spontaneously to normal rhythm in utero. In 3 fetuses the atrioventricular block persisted during labor and after the birth. All these 3 fetuses had heart malformations diagnosed in utero. One baby had a coarctation of the aorta, atresia of the mitral valve, single ventricle and an atrial septum defect. It died at the age of 3 weeks. One baby had a large atrial septum defect and an insufficiency of the pulmonary valve, and died 2 weeks postnatally. One baby had a common atrioventricular foramen - a single atrium, and a ventricular septum defect, an aberrant inlet of superior vena cava and a hypoplastic left ventricle. This baby died 1 week after birth. At the time of the intra-uterine blood flow measurements, the 4 fetuses did not show any signs of heart insufficiency such as ascites, hydrothorax, pericardial effusion or liver enlargement.

The fifth case was a 40-year old multipara who was referred to the labor ward because of fetal bradycardia detected after 42 postmenstrual weeks (the pregnancy was the only one not ultrasonically dated in this material). The blood flow in the thoracic descending aorta was

TABLE III. Aortic blood velocity waveform parameters in fetuses with atrioventricular block and ventricular extrasystoles.

Atrioventricular block (n=4)		Ventricular extrasystoles (n=3)				Normal values
		Fetus no.	Extra-systole	First post-extra-systolic beat	Period of regular rhythm	
Vpeak (cm·s ⁻¹)	Mean	1	96.3	145.3	139.0	115.6
	+ SD	2	54.9	145.6	93.5	+19.0
	-	3	65.0	143.4	109.0	-
Rising slope	Mean	1	19.9	16.4	29.2	29.9
	+ SD	2	60.0	41.6	31.5	+4.9
	-	3	29.0	26.2	27.1	-
Acceleration (cm·s ⁻²)	Mean	1	699	936	1562	1514
	+ SD	2	828	1943	1121	+292
	-	3	679	1449	1160	-
Acceleration time percentage	Mean	1	13	27	18	19.2
	+ SD	2	11	20	19	+2.2
	-	3	13	22	22	-
Pulsatility index	Mean	1	2.32	2.08	2.29	1.96
	+ SD	2	4.10	3.33	2.47	+0.31
	-	3	2.47	2.34	2.27	-

77 ml $\cdot$ min $\cdot$ kg $^{-1}$ and the mean blood velocity 11.3 cm $\cdot$ s $^{-1}$. Negative diastolic velocities were recorded in the descending thoracic aorta. Peak velocity was normal (127.1 cm $\cdot$ s $^{-1}$) but RS (68.8) and the systolic acceleration (1458.6 cm $\cdot$ s $^{-2}$) were higher than the normal values. Real-time ultrasound examination revealed a dilated IVC, a large ventricular septum defect, hydrothorax and ascites. The fetus died in utero and autopsy confirmed a large ventricular septum defect. The fetus had a phenotype suspected of chromosomal aberration (trisomy 21). This was not confirmed by chromosomal analysis due to technical failure.

Ventricular extrasystoles (Table III)

Three fetuses had extrasystoles of ventricular origin. In the IVC, regular pulsations of the blood velocity were recorded, reflecting the atrial contractions; concomitant with the premature ventricular contractions, high amplitude negative velocities occurred. The aortic velocity waveform analysis revealed lower values of the peak velocity during extrasystoles than during the periods of regular rhythm. The highest peak velocity was found in the first postextrasystolic beat. A similar relation was found for the systolic acceleration. The averaged mean blood velocities in the 3 fetuses were 25.1, 22.7, and 27.2 cm $\cdot$ s $^{-1}$, respectively, and the volume blood flow 186, 180, and 190 ml $\cdot$ min $^{-1}\cdot$ kg $^{-1}$, respectively. In 2 cases the arrhythmia persisted postnatally.

DISCUSSION

The clinical relevance of fetal heart arrhythmia has been discussed in many papers.^{3,14,15,16,17} Previously, fetal arrhythmia was largely ignored, but recently, based on the experiences from larger series of cases,^{3,15,16,17} recommendations have been made for the careful evaluation of fetuses having an irregular heart action. Technical developments in ultrasound technique have made possible non-invasive intrauterine examination of heart morphology¹⁸ and function.³ Intro-

duction of the pulsed Doppler technique into fetal studies has facilitated further improvements in hemodynamic evaluation.^{2,8,9}

The method combining real-time ultrasonography with pulsed Doppler technique for measurement of fetal blood flow was tested in an animal model against electromagnetic flowmeters and was found reasonably accurate.¹⁰ In the present material, aortic blood flow was within the normal range in all but one fetus. A similar finding was published by Tonge et al.⁸, who established heart rate limits (50 and 250 beats·min⁻¹, respectively) beyond which the performance of fetal myocardium is impaired. In our material, the term fetus that had a pathologically low aortic blood flow had total atrioventricular block and a pulse rate of 66 beats·min⁻¹. The heart block was associated with a large cardiac malformation and there were ultrasonic signs of intrauterine heart failure (ascites, hydrothorax). The other four fetuses with atrioventricular block had pulse rate within a comparable range, but no signs of cardiac failure; all of them had normal values of the aortic flow. Experience with this group of fetuses suggests that estimation of fetal aortic blood flow can be used to diagnose intrauterine heart failure. Earlier, we have demonstrated that, in cases where intrauterine treatment with digoxin is indicated, the therapeutic effect can be monitored by serial estimation of the fetal aortic flow.¹⁹

A very consistent finding in all fetuses having extrasystolic beats was the increased peak maximum velocity during the first postextrasystolic beat. This was mentioned already in our first report on blood flow examinations in fetuses with cardiac arrhythmia²⁰ and later confirmed by others.⁷ Mean aortic stroke volume was calculated to be 23% higher for postextrasystolic beats than for regular rhythm beats in the same fetus.⁷ In the present material, the aortic peak velocity was significantly correlated to the preceding beat-to-beat interval in the fetuses with extrasystoles. Tonge et al.⁸ found a similar relation between heart rate and aortic peak mean velocity and stroke volume in fetuses with bradycardia and tachycardia. In the present study, the peak maximum velocity was increased in cases with atrioventricular block (Table III) and decreased in cases with tachycardia (Table II).

All this evidence indicates that there is a close relation between the ventricular filling phase and flow characteristics of the following beat. An increased ventricular filling causes an increased stretching of the heart muscle, resulting in potentiated contraction and augmented stroke volume, according to Frank-Starling's law.²¹

The existence of the postextrasystolic potentiation according to the Frank-Starling's law was further supported by the fact that in the group of fetuses with supraventricular extrasystoles, there was a significant correlation between the preceding beat-to-beat interval and the systolic acceleration and between the beat-to-beat interval and the RS. In an experimental study on fetal lambs, the RS of the blood velocity recorded from the descending aorta was correlated to the myocard contractility measured as the first derivative of the maximum dP/dt in the left ventricle;²² this was true when the peripheral vascular resistance (characterized by the PI) was unchanged. In the human fetus it is unlikely that peripheral vascular resistance would change during one single extrasystole and the RS can be therefore considered to reflect the myocard contractility. The mean blood velocity and the blood flow in the group of fetuses with supraventricular extrasystoles were within the normal range, indicating the ability of the fetal heart to maintain normal circulation despite the hemodynamically less effective extrasystolic beats.

In the fetuses with atrioventricular block, the dissociation of the atrial and ventricular contractions was clearly demonstrated in the blood velocity traces recorded from the IVC and descending aorta. The shape of the velocity waveform recorded from the descending aorta was different from that in fetuses with normal heart rate. The duration of the acceleration phase was longer than in fetuses with normal rhythm (92.7 vs. 84.9 msec, respectively). The acceleration time percentage, however, was shorter in the atrioventricular block group than in the normal fetuses (10.3 vs. 7.7%, respectively). In the 4 fetuses with aortic blood flow within the normal range, the forward flow was maintained throughout the diastole. The above described changes in the velocity waveform and the finding of an increased RS and peak maximum velocity indicate an increased stroke volume resulting in a normal

aortic flow despite the very low heart rate. The PI was high in this group of fetuses. However, the interpretation of this finding is uncertain, as the value of the PI as a parameter of the peripheral vascular resistance for heart rate outside the normal range has yet not been established.

In fetuses with ventricular extrasystoles, no consistent pattern could be discerned in the appearance of the aortic velocity waveform. This might be due to the varying hemodynamic efficiency of ventricular extrasystoles, which probably depend on the timing and localization of the focus from which the extrasystole is initiated. In the blood velocity traces from the IVC, some of the deflections had a high negative amplitude. These deflections probably reflected atrial contraction against closed atrioventricular valves during premature ventricular contraction.

The type of the compensatory pause following extrasystole (complete or incomplete) can be judged from the time analysis of the aortic velocity traces. This analysis can facilitate differentiation between supraventricular and ventricular extrasystoles. However, the time analysis is not always conclusive, especially not in cases with nodal extrasystoles or with early occurring supraventricular extrasystoles causing a prolonged acceleration phase in the first postextrasystolic aortic beat.

In our material, 6 fetuses had cardiac malformations, 2 in the group with supraventricular extrasystoles and 4 in the group with atrioventricular block. In one fetus with atrioventricular block, an abnormally low aortic blood flow was recorded and, at the same time, there were ultrasonic signs of cardiac failure. In the remaining fetuses with cardiac malformation there was normal aortic blood flow and no characteristic changes in the aortic blood velocity traces. Obviously, due to the specific features of the fetal circulation, the fetal heart is capable of maintaining an adequate circulation despite the malformation. Therefore, in order to detect the possibly existing cardiac malformation, a careful ultrasonic study of the heart anatomy should be undertaken in all cases of fetal cardiac arrhythmia.

The present paper has described the hemodynamic features of various types of fetal cardiac arrhythmia. Changes in myocardial performance during the arrhythmias made this particular group of fetuses a useful model for the study of fetal circulatory physiology. The results of the blood flow studies demonstrated the very effective compensatory mechanisms of the fetal heart. In cases where these compensatory mechanisms are failing, this can be detected by the present method. The method can be thus of clinical use in the management of fetuses with cardiac rhythm disorders and in evaluating the effects of intra-uterine treatment, when indicated.

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FETAL CARDIAC ARRHYTHMIA

Clinical Outcome in 113 Cases

Göran Lingman,* Nils-Rune Lundström,** Karel Maršál* and Sten Ohrlander⁺

From the *Department of Obstetrics and Gynecology, General Hospital, University of Lund, Malmö, the ** Department of Pediatric cardiology, University of Lund, Lund, and the ⁺ Department of Obstetrics and Gynecology, Central Hospital, Helsingborg, Sweden

ABSTRACT

In 113 cases of fetal cardiac arrhythmia, i.e. 94 with supraventricular arrhythmia, 5 with atrioventricular block and 14 with ventricular arrhythmia, the clinical outcome was studied and compared with the general pregnant population. The arrhythmia group was afflicted with a significantly increased frequency of congenital malformations, 6.2% vs. 2.0%; fetal distress in labor, 20.4% vs. 13.5%; perinatal mortality, 3.5% vs. 0.7%; and neonatal mortality, 1.8% vs. 0.1%. In 4 cases, pharmacological cardiac treatment was needed in utero due to fetal heart failure. Fetuses with cardiac arrhythmia thus constitute an obstetric and pediatric high-risk group that should be subjected to an intensified supervision to detect fetal heart failure or fetal distress. When indicated, these complications can be treated in utero.

Key words: human fetus, cardiac arrhythmia, pregnancy outcome

In daily clinical practice, fetal arrhythmia is often ignored, despite a number of case reports indicating serious consequences for the fetal condition denoted by certain types of arrhythmia (1,2,3). The present paper summarizes our experience of the clinical outcome of 113 fetuses with different types of heart arrhythmia.

MATERIAL AND METHOD

Over a 6-year period (1979-84), 113 cases of irregular fetal heart sounds detected at six obstetric units in southern Sweden were referred to the authors for evaluation. Clinical data were collected from the patients' records at the antenatal clinics and the labor wards. Relevant maternal and neonatal background data are given in Table I. The newborns were examined by pediatricians and/or pediatric cardiologists.

For diagnosis and classification of the fetal heart arrhythmia, we used either fetal abdominal ECG or blood flow measurement in the descending aorta and inferior vena cava of the fetus, or both these methods (4). Fetal blood flow was measured with a combined real-time and pulsed Doppler ultrasound technique (5); the results of the hemodynamic evaluation will be reported elsewhere (Lingman & Maršál, submitted 1985). Fetal cardiac arrhythmias were classified under one of three main headings: supraventricular arrhythmia, atrioventricular block (AV-block), and ventricular arrhythmia. Fetal heart anatomy was examined with a real-time linear array ultrasound scanner (ADR 2130, Advanced Diagnostic Research Corp., Tempe, Arizona; Hitachi EUB 22, or Hitachi EUB 25 M, Hitachi Medical Corporation, Tokyo, Japan). When indicated, fetal heart treatment was performed by giving digoxin to the mother (6).

Statistical evaluation was performed with a test for comparison of a percentage based on a large sample with a known standard (7). 95% confidence limits were established according to Scientific Tables (8).

Table I. Maternal and neonatal background parameters in 113 pregnancies with fetal heart arrhythmia

Type of arrhythmia	Maternal parameters			Neonatal parameters		
	N	Maternal age (years)*	Nulliparae/multiparae	Male/female	Gestational age at birth (weeks)*	Birth weight (g)†
Supraventricular arrhythmia	94	27 (18-43)	47/47	41/53	40.0 (33-42)	3283 (742)
Atrioventricular block	5	31 (24-40)	0/5	3/2	40.5 (37-42)	2970 (303)
Ventricular arrhythmia	14	26 (20-43)	7/7	3/11	38.0 (37-40)	3605 (598)
Total	113	27 (18-43)	54/59	47/66	40.0 (33-42)	3309 (720)

* Median and range. †Mean and SD.

RESULTS

Of the 113 fetuses with cardiac arrhythmia, 94 had supraventricular arrhythmia, 5 had atrioventricular block and 14 ventricular arrhythmia. Details concerning the time of diagnosis and frequency of the pharmacological treatment are presented in Table II. Compared with the general population, the study groups showed a significantly higher frequency of perinatal and neonatal mortality, congenital malformations and fetal distress in labor (Tables III and IV).

In the following, a more detailed description of the clinical outcome is presented.

Supraventricular arrhythmia

Of the 94 fetuses that had supraventricular arrhythmia, 84 had supraventricular extrasystoles, 6 had paroxysmal supraventricular tachycardia, one fetus had an atrial flutter and 3 had sinus bradycardia.

Supraventricular extrasystoles. Of the 84 fetuses that had supraventricular extrasystoles, 2 died in utero due to placental abruption, one infant died at the age of 6 months of muscular dystrophy, one fetus appeared at the post partum examination to have a ventricular septum defect and a chromosomal aberration (trisomy 18). The remaining newborns were healthy.

Paroxysmal supraventricular tachycardia. Two out of the 6 fetuses with tachycardia had concomitant heart enlargement and were treated with digoxin in utero, with successful conversion to normal rhythm. The remaining 4 fetuses showed no intra-uterine signs of heart insufficiency. Two of them converted spontaneously to sinus rhythm in utero. In the other 2 cases, the tachycardia was still present after birth and the newborns were treated with digoxin and propranolol, whereafter the rhythm normalized and the treatment could be terminated after 6 months.

Table II. Time for detection of the fetal arrhythmia and frequency of drug therapy

Type of arrhythmia	N	Diagnosis of fetal arrhythmia			Arrhythmia persisting postpartum	Drug therapy	
		Gestational age (weeks)*	Antepartum	Intrapartum		In utero	Post-natally**
Supraventricular arrhythmia	94	35 (21-42)	90	4	30	3	7
Atrioventricular block	5	34 (29-40)	5	0	4	1	2
Ventricular arrhythmia	14	37.5 (25-42)	11	3	6	0	0
Total	113	35 (21-42)	106	7	40	4	9

* Median and range.

+ Digoxin.

++ Digoxin and/or propranolol.

Table III. Outcome of pregnancies with fetal cardiac arrhythmia

Outcome of pregnancy	Supraventricular arrhythmia (n=94)	Atrioventricular block (n=5)	Ventricular arrhythmia (n=14)	Total (n=113)
Complications of pregnancy				
Abdominal pain	5	1	1	7
Abruptio placentae	4	0	0	4
Growth retardation	9	0	0	9
Pre-eclampsia	8	1	1	10
Fetal and neonatal outcome				
Fetal distress in labor	28	0	4	32
Apgar score < 7 1 min	16	2	2	20
< 7 5 min	8	2	0	10
Operative delivery *	23	1	1	25
Malformation	4	3	0	7
Stillbirth	2	1	0	3
Neonatal deaths				
< 7 days postpartum	1	0	0	1
8-28 days postpartum	0	2	0	2

* Includes vaginal instrumental extractions and cesarean sections.

Table IV. Outcome of pregnancies with fetal cardiac arrhythmia and in general pregnant population

Outcome	Fetal cardiac arrhythmia (n=113)		General population	Significance of difference
	(%) 95% confidence limits (%)			
Perinatal mortality	3.5	1.0-8.8	0.7	p<0.001
Neonatal mortality (8-28 days)	1.8	0.2-6.5	0.1	p<0.001
Congenital malformation	6.2	2.5-12.4	2.0	p<0.01
Fetal distress in labor	28.3	20.9-38.6	13.5	p<0.001
Operative deliveries	22.1	14.9-31.0	17.5	p>0.05

Atrial flutter. The only case of the atrial flutter was found in the fetus of a 31-year-old healthy primigravida. A tachycardia of 190 beats/min was first heard in the 33rd gestational week. The patient was referred to us in the 37th week of gestation. An ultrasound examination then revealed slight fetal ascites; no abnormal heart anatomy was seen. A 2:1 blocked atrial flutter was diagnosed and intra-uterine digoxin treatment was started. Both the arrhythmia and the ascites vanished after 3 days of treatment. After 5 days of regular rhythm the atrial flutter recurred and the infant was delivered by cesarean section on the indication recurrence of the arrhythmia in a full-term fetus and diminishing fetal aortic blood flow. The diagnosis of the atrial flutter was confirmed in the newborn, which was otherwise in good condition. The heart rhythm normalized after 2 days of additional digoxin therapy. The digoxin medication was terminated after 4 months, whereafter the child stayed healthy.

Sinus bradycardia. In the 3 fetuses with sinus bradycardia, a heart activity of 95-110 beats/min was found. All 3 babies were born vaginally; 2 were healthy, but the third died within one week. At autopsy,

agenesia of corpus callosum, cardiomyopathy with lipid infiltration of the myocardium, hypospadia and retention of the testicles were found.

Atrioventricular block

Of the 5 fetuses with AV-block, 2 had AV-block grade II which converted spontaneously into regular sinus rhythm in utero. During labor both fetuses had normal heart frequency. One of the newborns had normal heart rhythm and remained healthy (follow-up 4 years). In the second infant the AV-block recurred immediately after birth, this time as a total AV-block and the infant died at the age of one month of heart insufficiency due to heart malformation (tricuspid ostium malformation, atrial and ventricular septum defect and stenosis of the pulmonary artery).

The remaining 3 fetuses had AV-block grade III. One of them died in utero with signs of heart failure (fetal ascites and hydrothorax), and with a large ventricular septum defect. The phenotype was typical for trisomy 21, though due to a technical failure this could not be confirmed by chromosome analysis. The second fetus with a grade III AV-block was born spontaneously at term; the newborn was in good circulatory condition despite the persisting arrhythmia. In postnatal life the infant did not need any therapy and developed normally. In the last fetus of this group, a grade III AV-block was diagnosed in the 33rd week of gestation. The fetus presented with ultrasonic signs of cardiac failure (heart enlargement, ascites and hydrothorax) and the ultrasound examination revealed a heart malformation (an atrial septum defect, aberrant entering of the inferior vena cava). Because of the difficulty in assessing in utero the operability of the heart malformation, digoxin treatment was started. The hydrothorax disappeared and the ascites diminished; in the 37th week of gestation the patient gave birth vaginally and the newborn was circulatory compensated. Further investigation indicated an inoperable heart malformation (common atrioventricular foramen, hypoplastic left ventricle and aberrant inlet of the superior vena cava). After discontinuation of the cardiotonic therapy, the infant died.

Ventricular arrhythmia

The 14 fetuses in this group had ventricular extrasystoles. One fetus was growth-retarded and in two pregnancies there were signs of pre-eclampsia. Four fetuses showed signs of distress in labor, but there was no perinatal mortality. The postnatal development of all newborns was uneventful.

DISCUSSION

The predominant type of arrhythmia in the present material was the supraventricular, consisting mostly of supraventricular extrasystoles. These did not seem to have any negative circulatory effects. Nevertheless, they were associated with an increased frequency of fetal distress and complications of pregnancy, in contrast to the findings in earlier studies (9,10,11). There were 2 stillborns in the group, due to abruptio placentae. Wladimiroff et al. (12) found congenital heart malformations also in cases of extrasystoles and sinus bradycardia, a finding confirmed in the corresponding types of arrhythmia in our material.

The tachyarrhythmias require particular attention as they can cause fetal heart failure (13,14). In the present material, 6 cases of paroxysmal supraventricular tachycardia and 1 atrial flutter were found, of which 3 required intra-uterine digoxin treatment because of signs of heart failure.

The group with AV-block had the highest mortality total. Three fetuses died in utero or neonatally, death being caused by heart malformation. No serological or clinical signs of maternal connective tissue disease were found (15).

In the group with ventricular arrhythmia, no malformations were seen and there was neither intra-uterine nor neonatal mortality.

In the whole material there was a 5-fold perinatal mortality and an 18-fold neonatal mortality compared with normal infants (Table IV). The perinatal mortality in our material was due to placental abruption in 2 cases and heart malformation in one case. The neonatal mortality was due to various heart malformations. There was also an increased frequency of fetal distress and pregnancy complications. Altogether, 4

cases of heart malformation were found, of which 3 were in the group with AV-block. One case of ventricular septum defect and one case of fatal cardiomyopathy were found in the group with supraventricular arrhythmia.

Altogether 4 cases of intra-uterine cardiac failure occurred. All were successfully treated in utero. It has been suggested that all isolated supraventricular tachyarrhythmias should be treated in utero because of the imminent risk of heart failure when the fetal heart rate exceeds 240 beats/min (14). However, treatment is probably not necessary in all such cases, provided the hemodynamic condition of the fetus is satisfactory when monitored with blood flow measurements and real-time ultrasound examinations.

In 72% of fetuses the arrhythmia disappeared prenatally. During birth, fetal ECG could be recorded from the fetal scalp by means of a scalp electrode. The cardiotocographic recordings were often impaired by the fetal arrhythmia and were consequently nonconclusive as regards fetal asphyxia. Therefore, during labor, the fetus should be monitored with intermittent fetal scalp blood sampling.

Opinions consistent with the present study concerning the increased frequency of fetal heart malformations connected with AV-block were expressed in earlier publications (9,10). In contrast to those studies, we have found an increased risk for fetal distress and presence of cardiac malformations also in cases of supraventricular extrasystoles. It is obvious that the patients with fetal cardiac arrhythmia constitute an obstetric and pediatric high-risk group. Our results emphasize the need to examine cases of fetal cardiac arrhythmia in order to establish the type of arrhythmia and the possible presence of concomitant complications. It is shown that these various perinatal complications can be then more adequately dealt with.

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INTRAUTERINE DIGOXIN TREATMENT OF FETAL PAROXYSMAL TACHYCARDIA CASE REPORT

BY

G. LINGMAN

S. OHRLANDER

Department of Gynaecology and Obstetrics

AND

P. OHLIN

Department of Clinical Physiology, Hospital of Helsingborg, Sweden

Summary

A patient with fetal paroxysmal supraventricular tachycardia (PST) with a heart rate above 300 beats/minute in the 29th week of pregnancy is described. The fetus showed signs of severe cardiac failure and was, therefore, digitalized by giving the mother 0.5 mg digoxin intravenously on the first day and then 0.25 mg oral digoxin daily throughout the pregnancy. After one day a normal rhythm was observed. The patient was delivered of a healthy girl after 38 weeks of pregnancy. Digoxin concentrations in samples of umbilical cord vein and artery, intrapartum scalp capillary, and amniotic fluid were almost equal, but somewhat lower than in simultaneously obtained maternal serum. Intrauterine digoxin treatment of fetuses with PST is discussed.

ABOUT 50 cases of paroxysmal supraventricular tachycardia (PST) of the fetus have previously been reported (Vallerius and Ramsoe-Jacobsen, 1978). Until a few years ago, these arrhythmias were considered to be well tolerated by the fetus (Levkoff, 1969). However, recent reports suggest that PST might lead to severe cardiac insufficiency of the fetus and the newborn (Hedvall, 1973; Vallerius and Jacobsen, 1978; Schreiner *et al*, 1978). Moreover, some fetal deaths involve severe hydrops without evidence of blood group incompatibility, these deaths might have been caused by cardiac insufficiency due to arrhythmias.

The highest fetal heart rate associated with PST previously reported was 300 beats/minute (Hochberg *et al*, 1976). When the fetal heart rate persistently exceeds 230 beats/minute the fetus is

significantly at risk (Vallerius and Jacobsen, 1978). Although digitalis should be the appropriate treatment for PST in the fetus, the effect of long-term treatment during pregnancy has not been examined. Digoxin crosses the placenta and almost the same concentrations are found in the fetus as in the mother (Rogers *et al*, 1972; Saarikoski, 1976). Treatment of the fetus is therefore possible and might be effective.

CASE REPORT

Eleven weeks before term, irregular fetal heart sounds were noted in a 25-year-old primipara. Auscultation revealed a marked irregularity of the fetal heart sounds but the heart rate seemed to be within the normal range. The cardiotocogram (CTG) revealed a frequency of about 140 beats/minute, normal variability and no

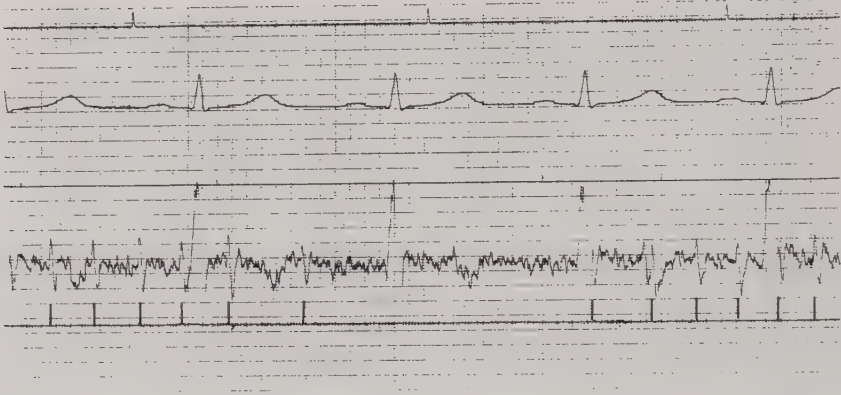


FIG. 1

Fetal ECG showing paroxysmal tachycardia. Recordings from above: Time in seconds, maternal ECG, indifferent line, abdominal ECG, line with fetal QRS-complexes marked.

decelerations. An abdominal fetal electrocardiogram (ECG) showed PST with a ventricular rate of about 300 to 400 beats/minute and occasional pauses lasting one second without any visible QRS-complexes (Fig. 1). The fetal ECG was repeated the next day with the same result. Ultrasound investigation showed a heart that almost filled the whole thorax of the fetus, and with valves that moved irregularly.

The fetus was digitalized by giving the mother 0.25 mg of digoxin intravenously twice on the first day and then 0.25 mg of oral digoxin daily. After the first day of treatment, regular fetal heart rhythm was heard on auscultation and after the second day, an abdominal ECG was normal with a regular rhythm and a frequency of about 150 beats/minute. The digoxin treatment was continued throughout the pregnancy. Digoxin concentration in maternal serum was measured by a radioimmunoassay method and serial estimates gave values of 0.9 to 1.6 nmol/l which were within the therapeutic range. The abdominal fetal ECG was recorded once a week and remained normal. Ultrasound investigation showed that the size of the fetal heart was normal one week after the start of the treatment, and it remained normal until delivery. The fetal biparietal diameter increased at the

TABLE I
Digoxin concentrations in simultaneous samples from the fetus and the mother

Fetal sample	Digoxin concentration (nmol/l)	
	Fetal sample	Maternal serum
Amniotic fluid	1.1	1.6
Scalp capillary	0.9	1.6
Umbilical cord vein	1.0	1.1
Umbilical cord artery	0.9	1.1

normal rate, and maternal serum oestriol levels were within the normal range, indicating fetal well-being.

After 38 weeks gestation, the woman went into spontaneous labour. Direct fetal scalp ECG and CTG revealed a normal fetal heart rate and no arrhythmia. Repeated fetal scalp capillary pH values were normal. The patient was delivered vaginally after eight hours' labour of a female infant weighing 3050 g with an Apgar score of 8 at five minutes. Simultaneous samples from the fetus and mother were obtained during and after delivery and analysed for digoxin concentration (Table I). IgM values and indices of thyroid,

function in umbilical cord blood were normal. Immediate postpartum examination by a senior member of the neonatal unit revealed no signs of cardiac insufficiency or valvular abnormality. The neonatal ECG showed a normal heart rate and no signs of arrhythmia. A chest X-ray was normal. The infant was supervised in the neonatal unit for one week. There were no cardiac signs. The digoxin therapy of the baby will be continued for six months.

DISCUSSION

Although several instances of PST in the fetus have been previously reported, no one, as far as we know, has treated the fetus. This possibility has been discussed, when infants have been delivered, dead or alive, with signs of severe cardiac failure (Vallerius and Jacobsen, 1978).

Our fetus had the highest PST ever reported with a ventricular frequency of 300 to 400 beats/minute. Moreover, there were obvious signs of severe cardiac insufficiency with marked heart enlargement at the ultrasound examination. Without treatment, the fetus would probably have died. Delivery at this early gestational age (29 weeks) carries a high risk of pulmonary complications with pre-existing cardiac insufficiency. We considered it necessary to attempt the intrauterine treatment of the fetus with digoxin.

The fetus was digitalized by giving the mother the recommended adult dosage of digoxin and this resulted in a therapeutic concentration of digoxin in the maternal serum. The concentrations of digoxin at delivery in fetal blood and amniotic fluid were somewhat lower. However, the affinity of digoxin for the infant myocardium is higher than that of the adult (Wettrill, 1976). The concentration of digoxin in the fetus was obviously therapeutic as the heart rate became normal and the arrhythmia disappeared

after one day of treatment. The signs of fetal heart failure also disappeared. During the remaining nine weeks of pregnancy digoxin treatment was maintained and the fetal ECG showed normal heart frequency and regular rhythm until and after birth.

Investigation is indicated if irregular fetal heart sounds are detected during pregnancy. It is important to note that a normal antenatal abdominal CTG can be associated with a severe arrhythmia with a high ventricular rate. The explanation may be that only some of the ventricular beats are haemodynamically efficient, leading to proper opening and closure of the aortic valve. An abdominal fetal ECG allows the diagnosis of PST. If the frequency is high, intrauterine digitalis treatment may be life-saving.

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